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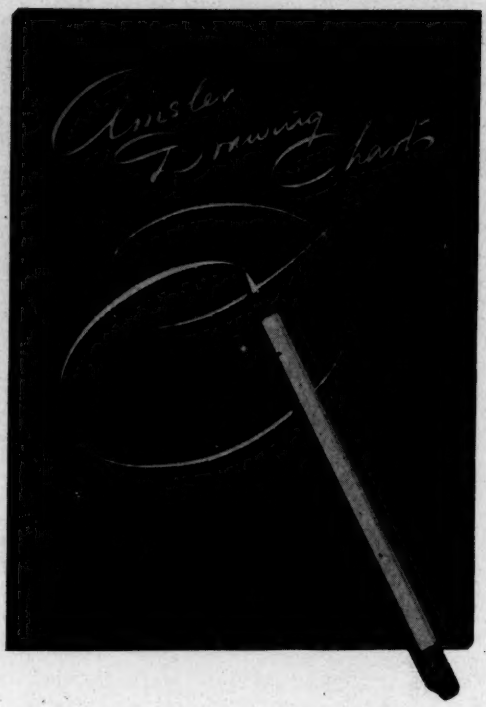

Supplementary to the Manual of Amsler Charts, this is an exact reproduction of Chart No. 1 but has a washable surface.

Using a soft, non-greasy crayon, the patient can draw what he sees directly on to the chart. After the drawing has been transcribed to a recording chart, the drawing chart may be cleaned by means of a damp cloth.

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Brit. J. Ophthal. (1954) 38, 257.

COMMUNICATIONS

EFFECT OF AREA AND INTENSITY ON THE SIZE AND SHAPE OF THE ELECTRORETINOGRAM*

EXCLUSION OF STRAY LIGHT EFFECTS

BY

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SINCE Adrian and Matthews (1928) showed that the latent period of the optic nerve discharge can be influenced by the size of the area stimulated, the effect of area on the electroretinogram has been confirmed by a number of workers (Granit, 1933; Creed and Granit, 1933; Fry and Bartley, 1935; Boynton and Riggs, 1951).

The size and shape of the electroretinogram can be influenced in the same way by increasing the stimulated area as by increasing the intensity of the stimulus. Fry and Bartley (1935) stated that the effect of area was due almost entirely to stray light; they believed the effect of the focal area to be small. They performed the following experiment on the intact rabbit eye:

> Two adjacent bright areas were exposed alternately against a dark background. Since the amount of stray light was the same in each case and diffusely distributed over the retina, alteration could not affect it: each of the two retinal spots, however, should respond intermittently if the focal response were dominant. Actually, at fast rates of alternation, no response was obtained, and this finding was explained on the assumption that stray light, being constant and independent of the area stimulated, acted as a much more effective constant background than the alternating focal points, which were therefore believed to elicit only a negligible fraction of the *b*-wave.

Granit, Rubinstein, and Therman (1935) disagreed with this generalization. To test it they produced, on the retina of the excised and opened frog eye, two sharply focused spots, about 0·4 mm. in diameter and 0·3 mm. apart.

> Threshold stimuli were used to elicit a response of about 50 μV. In this case the two stimuli A and B together elicited a response only 10–15 per cent. less than the expected value of A+B. Stray light could thus account for only this percentage of the combined response. Nevertheless when one flash was made to succeed the other, the effect of the second was inhibited. They concluded that adjacent neurones also were influenced by some kind of physiological spread of the electrical response, while admitting of course the existence of stray light unless special precautions were taken to avoid it.

More recently Boynton and Riggs (1951) and Asher (1951) have emphasized that the retinal response is primarily aroused by stray light rather than

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by the focal area. If the stimulus is made to fall on to the blind spot, there is no significant difference between the response obtained and that elicited by stimulation of a nearby area of equal size. Their view appears to be that any effect of stimulus area on the electroretinogram is doubtful.

Our problem was to study the electroretinogram by a device completely excluding stray light at high intensities with the stimulated area varying in size. We also wished to ascertain the minimal area necessary for the appearance of a standard electroretinogram. In view of the practical application of electroretinography to clinical problems, information on this point has become highly desirable.

Method

Dark-adapted cats were used. They were anaesthetized with Nembutal 40 mg./kg. intraperitoneally, 4–6 ml. urethane 20 per cent. solution being added if needed. After removal of cornea and lens, the iris was cut radially to increase the size of the pupil and part of the vitreous body was gently removed. From a Philips tungsten band lamp run off high capacity storage batteries at a constant temperature of 2,800° K, a parallel beam was focused by means of a mirror and a lens into the opened eye. Ilford neutral filters were used to vary stimulus intensity. Silver silver-chloride electrodes ending in a cotton wick soaked in saline were applied to the limbus and nose of the animal, and the leads were taken to a condenser-coupled amplifier of long time constant and a cathode-ray tube. The sweep was synchronized with a photocell. Single flashes 1/10 sec. in duration obtained with the aid of an Ibsor shutter were given at 30-sec. intervals (60 sec. at maximal intensity). To avoid stray light on the retina special Perspex cones 1-2-3-5 mm. in diameter at the top were used, and their external surface was blackened in order to prevent leakage of light. Selection of these particular values was based on preliminary experiments. Calibration revealed that the amount of light per unit area was the same, whether the whole pupil was filled or one of the different cones was used.

After not less than 40 min. dark adaptation the experiment was begun by taking a control electroretinogram at maximum intensity (2,000–3,000 lux, the exact value determined in each case) with light filling the whole pupil. Then a cone was inserted and moved step by step by a Zeiss micromanipulator down to the retinal surface; records were then taken at different intensities. The experiment was discarded as soon as the retina lost sensitivity with reference to the control response with the cone absent. This often occurred through bleeding and retinal detachment.

To judge how far the cones had to be moved into the eye in order to reach the retinal surface, red marks were painted on them at different levels: preliminary adjustments were made in the light by observing the depth at which the cone was close to the retinal surface. It sometimes happened that the cone was pushed a little too deep; then the electroretinogram rapidly diminished, but it recovered its normal size when the cone was slightly raised.

In some experiments we used intermittent illumination obtained by means of a rotating sectored disk providing equal periods of light and darkness. The disk was turned by a Velodyne reversing motor generator (British Air Ministry type 74) controlled electronically (Enroth, 1952). Fusion frequency was measured with a resonance method, as described by Granit and Wirth (1953). A resonance meter (vibration analyser, made by the General Radio Corporation, U.S.A.) was set to respond to the required frequency, the flickering electroretinogram being recorded and indicated by the galvanometer needle of the resonance meter. As long as flicker was present resonance was obtained on this instrument. Disappearance of resonance signified fusion (see below).

Results

Records from one experiment are presented in Fig. 1: only the initial phases of the electroretinogram were recorded since these were the ones used for quantitative analysis. The electroretinograms were taken at different intensities with the light filling the pupil and with retinal spots 5 and 3 mm. in diameter. On the left a complete series shows normal electroretinograms over a wide range of intensities. Only at maximum intensity (2,050 lux) was a definite *a*-wave present. The *b*-wave then rose very steeply and exhibited an initial faster component. As the intensity was decreased, the amount of potential was less influenced to begin with than the rate of rise and the latent period. At low intensities the *b*-wave flattened out and its latency lengthened. On the right a number of records taken with restricted areas are presented for comparison. The most striking feature is that the size and shape of the electroretinogram were more abruptly affected by a decrease in intensity of the stimulus. This is best seen by comparing the electroretinograms at equal levels of intensity: at 246 lux, for instance, the shape of the *b*-wave was much more influenced by a restriction of area than at the maximum intensity, while at 64 lux there was also a considerable difference in the size of potential. Over the whole range of areas stimulated at higher levels of intensity, the *b*-wave exhibited wavy contours. The increased amplification makes the results at low intensities less certain from this point of view.

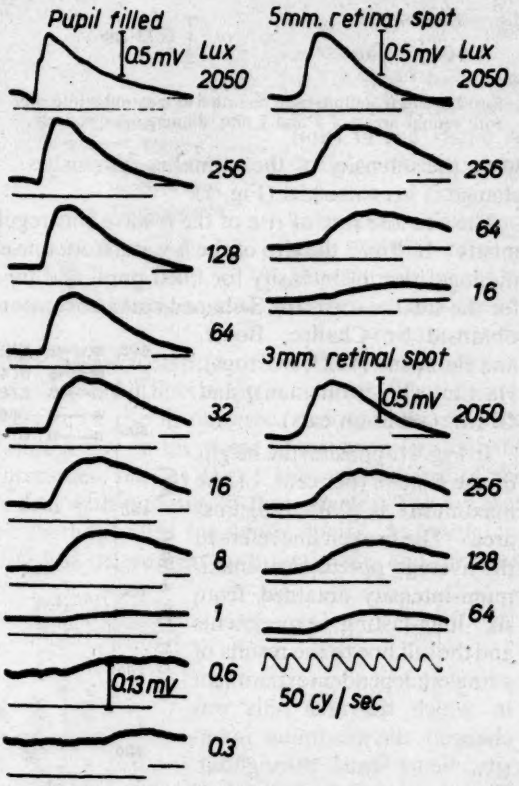

FIG. 1.—Electroretinograms recorded with cathode ray oscillograph at different intensities, with light filling the pupil, and with retinal spots of 5 and 3 mm. diameter respectively. Calibrations to 0·5 and 0·13 mV inserted. Duration of stimulus on second beam of cathode ray is given below each record.

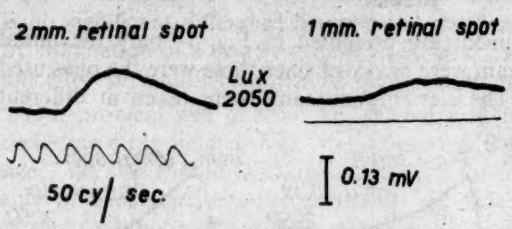

FIG. 2.—Electroretinograms recorded at maximum intensity with retinal areas of 2 and 1 mm. diameter respectively.

When smaller areas (1–2 mm. diameter) were stimulated, very slow small potentials could occasionally be recorded (Fig. 2), but then only in the very best animals and at maximum intensity.

As is well known the latent period of the electroretinogram increases when the intensity of the stimulus diminishes. With restricted areas this change is very marked (Fig. 1).

The size and rate of rise of the *b*-wave was regularly measured in all experiments. In Fig. 3 the size of the *b*-wave from one experiment is plotted against the logarithm of intensity for filled pupil and for the different areas. Except for the smaller areas the S-shaped curve corresponds well with that previously obtained by Chaffee, Bovie, and Hampson (1923, on frogs), Hartline (1925, on man), and Granit (1933, on cats).

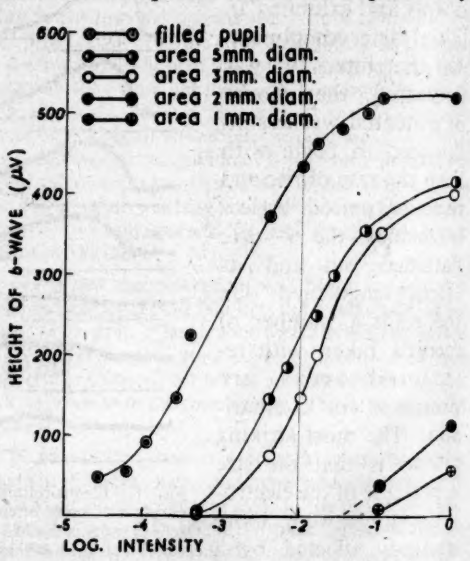

FIG. 3.—Height of *b*-wave from one experiment plotted against log. intensity for filled pupil, and areas of 5, 3, 2 and 1 mm. diameter.

In Fig. 4 (opposite) the height of the *b*-wave (per cent. of the maximum) is plotted against area. The broken line refers to the average potential at maximum intensity obtained from six long-lasting experiments and the full line to the results of a single independent experiment in which the area only was changed, the maximum intensity being used throughout. The six experiments involved tests with several variables. The agreement between the two curves is good. There is a steep rise up to around 7 mm.^{2} (3 mm. diameter); for greater areas the rise is slower. The difference in the range from 7 mm.^{2} to completely filled pupil (here marked ∞) is only about 24 per cent. If we assume the same relation to be roughly valid for the human electroretinogram and take the mean value of the scotopic *b*-wave as 0·36 mV (Karpe, 1946), then for an area of 7 mm.^{2}, that is at the knee in the curve, one should obtain 0·27 mV, a value well within the limits of normal variation. If the rate of rise is plotted against

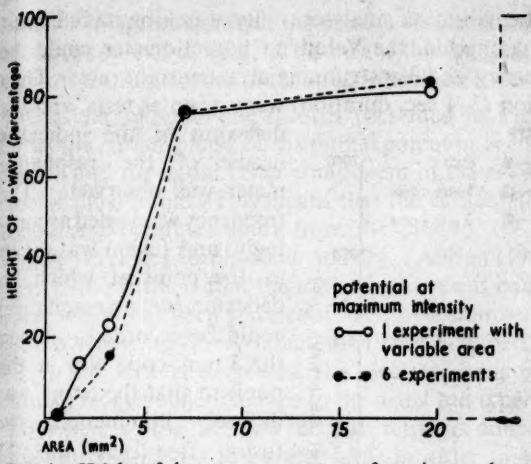

FIG. 4.—Height of *b*-wave as percentage of maximum plotted against area.

area (Fig. 5, below), the curve is very different. From 7 mm.² up to completely filled pupil it is of the order of 63 per cent. We shall deal with this point below.

To find some expression for the variations in the shape of the electroretinogram, the rate of rise was calculated. This function is the relation between the height of the *b*-wave and the so-called peak time (time interval from the beginning of the *b*-wave to its peak). The results from the six experiments were averaged and plotted (full lines in Fig. 6, overleaf), the ordinates (on the left) representing the rate of rise in mm./sec., and the abscissae the logarithm of intensity. The difference in the slope of the rate of rise of the curves is striking at high intensities, but, as Fig. 1 showed, the size of the *b*-wave did not vary a great deal with intensity at these levels. The *b*-waves merely became steeper when the light filled the whole pupil. At low intensities, however, the rate of rise was determined both by the size and the peak time of the potential. This is also emphasized by the shape of the curves relating amplitude of the *b*-wave (ordinates on the right) to log. I, plotted in the same figure (broken lines), showing how they depart at high intensities.

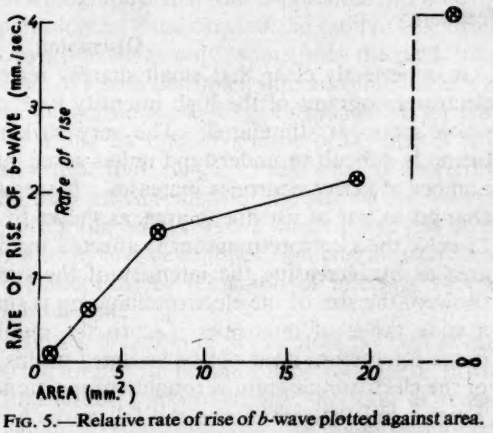

FIG. 5.—Relative rate of rise of *b*-wave plotted against area.

The effect of area on flicker fusion was tested by the resonance method developed by Granit and Wirth (1953). Leads from the amplifier were taken both to the vibration analyser and to the cathode-ray oscillograph. In order to have a ready check on the precise coincidence of frequency in analyser and flickering beam, the output from the photocell (which signals the flashes on the cathode-tube) was connected as

an alternative input to the vibration analyser. By watching its indicator needle with the photocell connected, the Velodyne potentiometer could be set for the required frequency and kept running at a constant rate. Then brief periods of illumination (3–4 sec. duration) were given as tests, and the deflexion of the indicator needle of the resonance meter was observed. The frequency was varied accordingly, and fusion was taken as the point at which no deflexion (*i.e.* no resonance) could be recorded. When the 3 mm.-cone was at the pupil so that the retina was diffusely illuminated, the fusion frequency was 73 flashes per sec. (intensity = 1,850 lux), but at the retinal surface the fusion fell to 14·3 flashes per second. This is in general agreement with the original observation by Granit and Harper (1930) on the effect of area in subjective flicker: over a large range of intensities an increase of stimulated area significantly augmented the fusion frequency.

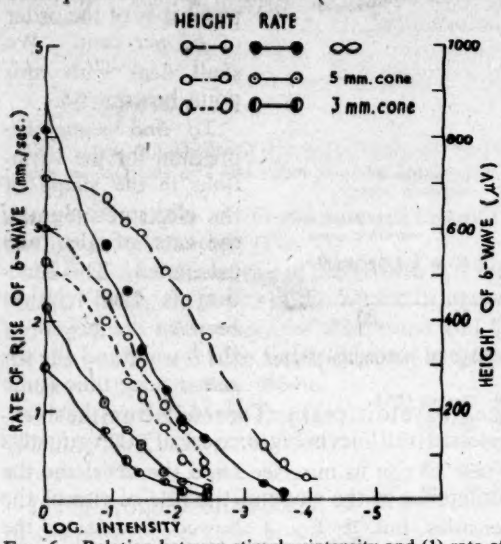

FIG. 6.—Relation between stimulus intensity and (1) rate of rise of *b*-wave (mm./sec.) (2) height of *b*-wave. Mean of six experiments.

Discussion

It is perfectly clear that small sharply restricted areas do not give small electroretinograms of the high intensity type such as are recorded when the whole retina is stimulated. The very striking effect of area upon flicker fusion is difficult to understand unless some integration takes place when the number of active neurones increases. It seems naturally related to the large changes in rate of rise due to area, as shown by Fig. 5. In the simple retina of *Limulus* the electroretinogram is affected in the same way by increasing the area as by increasing the intensity of the stimulus, but, as Graham (1932) showed, the size of the electroretinogram is simply proportional to area over a wide range of intensities, *i.e.*, to the number of ommatidia stimulated; hence interaction need not be assumed in this case. In the cat's eye the size of the electroretinogram is roughly proportional to area when this is less than 7 mm.^{2}, but the rate of rise and fall of the *b*-wave enables one to distinguish electroretinograms obtained from small areas from those obtained from large areas.

Recently Kuffler (1953), using the microelectrode technique, found receptive fields in the cat's eye of the order of 3–4 mm. diameter, a figure

which is in agreement with the present results, although Kuffler was in doubt about the spread of light. This means that integration may take place within areas of the same order of magnitude as those found by electroretinography.

Considering again the records presented in Fig. 1, it is evident that, as far as the earlier phase of the retinal potential is concerned, both the definite *a*-wave and the initial faster component of the *b*-wave are present only in the case of filled pupil. This means that the electroretinogram is then of a more cone-like type since, apart from the *a*-wave, the faster component of the *b*-wave is related to photopic activity. Adrian (1946), using monochromatic light, demonstrated that the initial faster rise is connected with cone activity, a fact which has been since confirmed by a number of authors (Riggs, Berry, and Wayner, 1949; Armington, 1952; Schubert and Bornschein, 1952). When the area is decreased the electroretinogram at maximum intensity changes from a cone-like type to the usual rod type. This may indeed be due, in our case, to the fact that the cat's retina is dominated by rods, so that the area illuminated has to be very large in order to give the cones a chance of influencing the average response.

From the point of view of clinical electroretinography some points are of interest. As a rule, the electroretinogram recorded for practical purposes is the response of the whole retina, to which both photopic and scotopic components contribute depending on the intensity of the light. In the intact eye it is impossible to produce sharply focused areas, since its optical system is far from perfect. The fact that a field of definite size has to be stimulated in order to give a retinal potential of definite amplitude and shape obviously means that a certain population of retinal units must be activated. It is a common observation in clinical electroretinography that the *b*-potential may be of normal amplitude in spite of pathological conditions of the retina. As a rule records are taken with one or two intensities only; sometimes the peak time is measured, but generally the rate of rise is not taken into account. Yet it is clear from our results that, within a considerable range of intensities, the size of the *b*-wave varies but little, whilst its rate of rise or peak time is still greatly influenced by changes within that range. Peak time is therefore likely to give more information than measurement of the size of the *b*-wave alone. The advantage of measuring the *b*-wave over a larger range has been emphasized by Burian (1953), who in one patient with unilateral glaucoma found the *b*-wave much more susceptible to reduction of intensity in the glaucomatous eye than in the normal one.

On the basis of the present results it is tempting to calculate the size of the area that must be stimulated in order to produce a detectable electroretinogram in man. This should indicate approximately the limit of sensitivity of the method. In the cat the average maximum potential developed is 0·75 mV when the light fills the pupil. With the 1-mm. cone the size of the *b*-wave, in the very best animals, is only 7 per cent. of the maximum, that is 0·052 mV. Assuming that the same relation holds for the human electro-

retinogram and taking the mean maximum value to be 0·36 mV, one would expect 0·025 mV for a receptor population functionally equivalent to an area of 0·78 mm². A potential of this order cannot be measured even if the base-line is perfectly steady.

Another point of interest in this connection is concerned with perimetry by electroretinography, which Monnier and Boehm (1947) claim to be possible. They stimulated various points in the retinal field using an area of 2° visual angle and a light intensity of 0·1 lumen. This means that, theoretically, the retinal area was less than 1 mm². They found that the amplitude of the *b*-wave was higher, the peak time shorter, and the *a*-wave more evident, as the stimulus was moved towards the centre of the visual field (from 60° to 20°). The size of the *b*-wave, however, was, on the whole, of the same order of magnitude as that obtained with non-localized stimuli. While their result probably signifies that the number of cones increases towards the centre, it nevertheless seems difficult to understand how the stimulus could have been restricted to the area under investigation, since the maximum potential the retina is likely to be able to develop with an area of 0·78 mm.² would be only about 0·02–0·03 mV, provided that *maximum intensity* were used. The results obtained by Boynton and Riggs (1951) and Asher (1951) with stimulation of the blind spot indirectly support this view. As already pointed out (Karpe, 1945; Wirth, 1950), electroretinographic perimetry would require threshold stimuli so as to avoid stray light effects at high intensities. It is, however, practically impossible to stimulate a *restricted* area with threshold intensity, since, as stated above, the potential is unlikely to be measurable even at maximum intensity. Admittedly our results were obtained with the cat's eye, but the human eye is not likely to be fundamentally different in this respect.

Summary

(1) A special device with Perspex cones, blackened on the outside and applied directly to the retina, was used to avoid stray light effects. Sharply focused spots of different diameters were thus produced in the opened cat's eye.

The sizes and shapes of the electroretinograms with standard leads were studied over a wide range of intensities for different areas.

Fusion frequency was measured by a resonance method recently described.

(2) In order to obtain an electroretinogram showing the characteristic features of the high-intensity response, it was necessary to use cones with a diameter of 3–5 mm. With smaller areas the response assumed the characteristics of the low-intensity electroretinogram. It was impossible to compensate for this effect of area by an increase of intensity.

In the best animals, a very small, slow response could be obtained with an area 1 mm. in diameter, but normally the lower limit was between 1·5 and 2 mm., and below this limit no electroretinogram could be recorded.

(3) Curves illustrating size and rate of rise of the *b*-wave as a function of area and intensity are given.

(4) Only high-intensity responses, elicited by large areas, could produce high-fusion frequencies in " flicker ".

(5) The significance of area is discussed with special reference to clinical electroretinography.

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SLIT-LAMP STUDIES ON THE FLOW OF AQUEOUS HUMOUR*†‡

BY

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IN the intriguing problem of the dynamics of aqueous humour there has recently been a shift in emphasis from what one might call the strictly biochemical approach, to a consideration of the bulk flow of aqueous humour utilizing electronic devices and tracer substances. This study is based on direct observation of the rate of flow of aqueous humour on 88 glaucomatous and normal patients.

Since the time of Ehrlich (1882) it has been known that fluorescein, instilled into the conjunctival sac, readily permeates the cornea and appears in the anterior chamber. Here its concentration may be measured by means of a slit lamp after the method of Amsler and Huber (1946). Use of these two observations has formed the basis for observing fluctuations in the rate of flow of aqueous humour wherein fluorescein is utilized as a tracer substance (Langley and MacDonald, 1952).

Technique

One drop of 5 per cent. fluorescein is instilled into the conjunctival sac. If no staining of the cornea is present after 5 minutes, one drop of 20 per cent. fluorescein is instilled. If, after an additional 5 minutes, there is still no staining, a drop of 0·5 per cent. pantocaine is instilled and the cornea is exposed to air for one minute, or until the corneal light reflex loses its lustre when another 20 per cent. drop is instilled. This is frequently necessary in young people or if tearing is excessive.

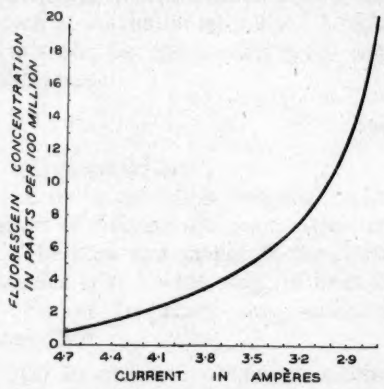

FIG. 1.—Conversion curve, showing relation of ampères to concentration of fluorescein.

Apparatus

The intensity of the resultant green flare in the aqueous observed with the Haag-Streit slit lamp is taken as an index of fluorescein concentration. The measurement is made by determining the minimal slit-lamp illumination necessary for the observer to recognize threshold green. By the use of this principle, accuracy is quickly attained with practice. Filament illumination is controlled by a variable rheostat in series with an ampmeter. Ampère readings, the measurement of current strength, are then converted into approximate fluorescein concentration in parts per 100 million (Fig. 1).

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†This paper was presented in part at the Sixteenth Annual Meeting of the Canadian Ophthalmological Society, Minaki, Ontario, June, 1953.

For greater accuracy in our present work, only one ocular of the slit-lamp is used. The latter is coupled to a control so that the observer has a monocular view of the fluorescein aqueous ray directly beside a control green (Fig. 2).

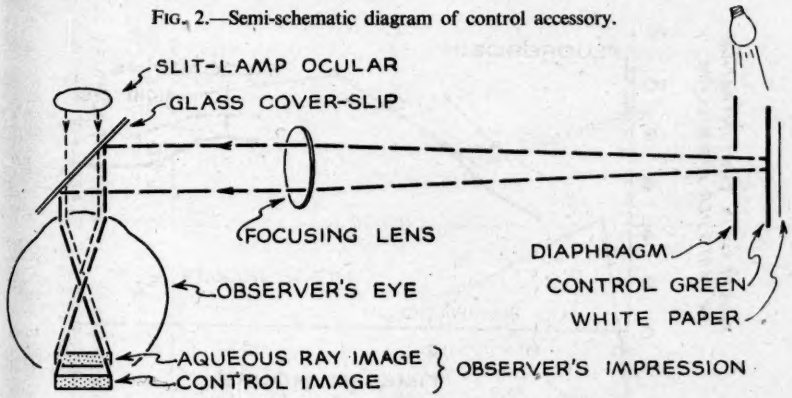
The control consists of a Wratten green (B -58) filter, mounted between glass cover-slips, lying on a white background and illuminated by a 6-watt lamp. The control lamp and the slit-lamp filament are on separate circuits, but are powered by the same main, so that small power fluctuations will affect each simultaneously.

The control is mounted on the end of a 15″ arm fixed by clamps to the slit-lamp ocular support. Mounted at 45° to the front of the ocular eyepiece is a glass cover-slip which reflects the rays of light from the control into the observer's eye. The control, illuminated at threshold green, is masked by a black diaphragm. A suitable slot is cut in the latter making the control resemble the aqueous ray under low power in size and shape.

In order to bring the aqueous ray and control to the same focus, a lens suited to the observer's refractive error is placed between the reflecting cover-slip and the control. It is important that the fluorescein aqueous ray be in sharp focus and that the observer's eye be centred properly behind the eye piece before a reading is taken.

The control image is brought into contact with the aqueous-ray image by rotation of the ocular with its fixed cover-slip. The width of the slit-lamp beam is determined at the beginning of the test by photo-electric cell calibration. Fluorescein readings are taken over the pupillary area of the patient's eye.

FIG. 2.—Semi-schematic diagram of control accessory.



Procedure

Altogether 117 eyes, 32 of which were normal, were examined. At the beginning of the test a careful search was made for aqueous veins and the most suitable ones were selected and observed throughout the test. The patients were allowed to read, drink fluids, and eat as desired. Fluorescein was instilled in the morning and the resulting concentration in the aqueous and the intra-ocular tension were recorded at frequent intervals throughout the day. The intra-ocular tensions were taken with a Schiötz tonometer after the instillation of a drop of 0·5 per cent. pantocaine solution. After the concentration of fluorescein in the aqueous had been observed for about 4 hrs, a miotic was instilled and its effect on the concentration of fluorescein was observed.

Results

In the Normal Eye.—The typical curve obtained from the study of 32 normal eyes is shown in Fig. 3. As reported in earlier work (Langley and MacDonald, 1952) the concentration of fluorescein in the aqueous humour gradually increased over the first 2½ hrs after instillation. At the end of this time a state was reached at which the amount of fluorescein entering the aqueous from the cornea was balanced by that leaving *via* Schlemm's canal, and other escape channels. After the " steady state " has been reached, the concentration of fluorescein gradually falls during the next 18 to 24 hrs until no traces are visible. In almost all cases this steady state was little influenced by the instillation of miotics.

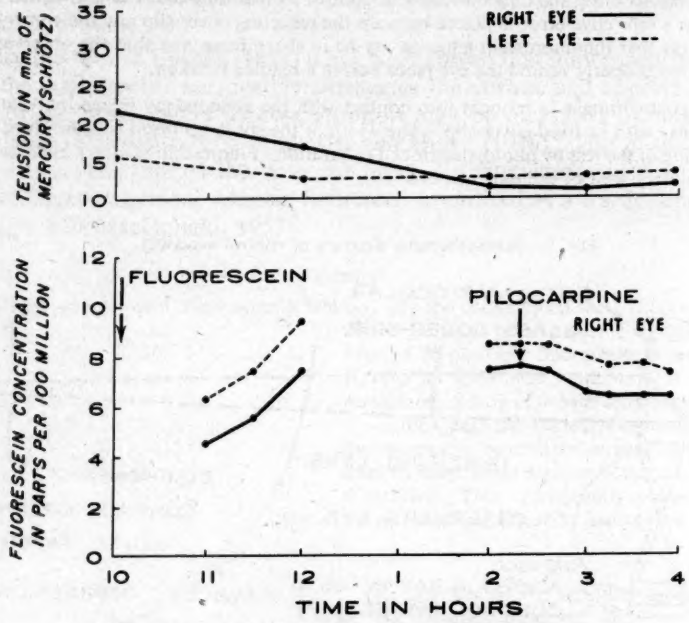


FIG. 3.—Concentration curve in normal subject.

In Glaucoma.—Concentration curves were observed in a total of 85 eyes. Most of the patients were referred from the glaucoma clinic of the Toronto General Hospital; the remainder from physicians interested in this investigation.

In 34 of the eyes studied after the instillation of 4 per cent. pilocarpine the curve shown in Fig. 4 (opposite) was obtained. Here it will be seen that there was a sharp drop in the concentration of fluorescein associated with a gradually falling tension. In sixteen eyes there was a similar drop in concentration without change in tension and in seventeen eyes the tension actually rose while the concentration of fluorescein fell (Fig. 5, opposite).

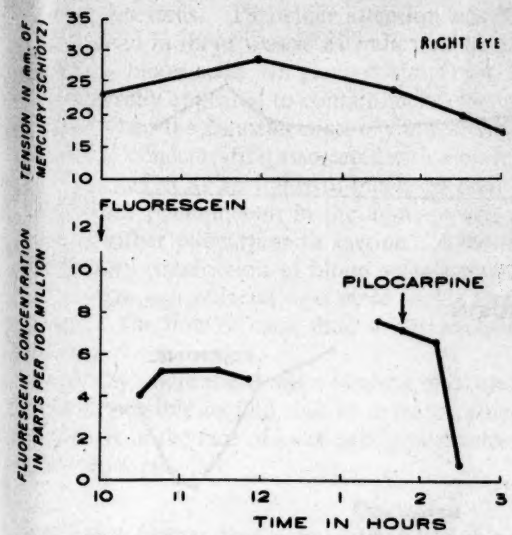


FIG. 4.—Effect of pilocarpine in glaucoma, showing fall in concentration and ocular tension.

Similar findings were observed after the instillation of 0·5 per cent. eserine. In four of the eyes treated a fall in the concentration of fluorescein was associated with a fall in the ocular tension. In three eyes a drop in concentration occurred without any change whatsoever in ocular tension, and in three eyes a drop in concentration was associated with a significant elevation in tension (Fig. 6, overleaf).

In eight eyes a marked drop in tension occurred after the instillation of

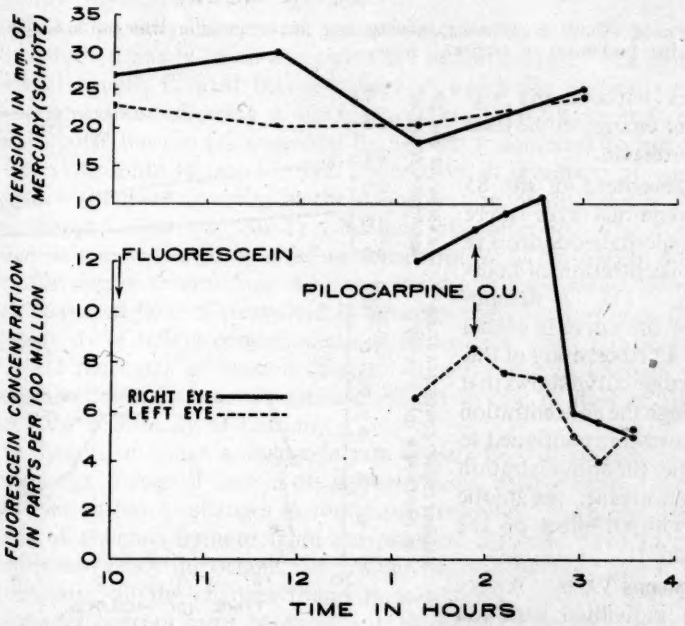


FIG. 5.—Curve in glaucoma, showing drop in concentration with rise in tension, after instillation of pilocarpine.

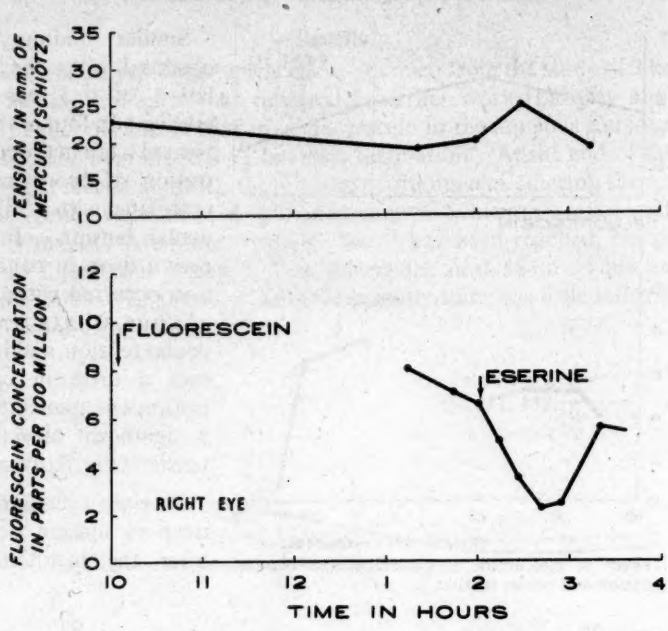


FIG. 6.—Curve in glaucoma, showing drop in concentration with rise in tension, after instillation of eserine.

miotics without any significant change in the level of fluorescein.

In seventeen of the 85 glaucomatous eyes there was a spontaneous drop in the concentration of fluorescein. Fig. 7 demonstrates the curve in such a case. Further study of this particular curve shows that although the concentration of fluorescein continued to fall after the administration of pilocarpine, the miotic was without effect on the tension.

Aqueous Veins.—A very great individual variation was observed in the prominence and configuration of

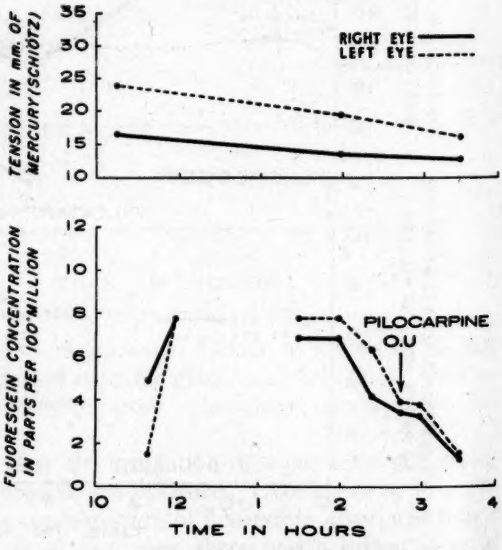


FIG. 7.—Concentration curve, in glaucoma, showing spontaneous drop in concentration, which continued after instillation of pilocarpine, although miotic did not affect tension.

the aqueous veins. Particular attention was paid to the relative rate of flow of clear fluid in these vessels as indicated by the rapidity of movement of occasional blood cells. In glaucomatous eyes, it was noted that the aqueous veins generally appeared to contain more clear fluid flowing at faster speeds at times when the concentration of fluorescein was falling or about to fall. This fall in concentration associated with a more rapid stream in the aqueous veins was taken as an index of increased bulk flow of aqueous humour.

The latter phenomenon in the aqueous veins usually followed the instillation of either pilocarpine or eserine. After the administration of eserine, a temporary constriction of blood vessels was also noted. The blood flow at this stage was reduced to a mere trickle frequently stagnating for several minutes. The flow of clear fluid in the aqueous veins, however, continued unabated.

Generally where there was a filtering bleb, clear sizable aqueous veins were almost impossible to find, but in cases in which the bleb had disappeared, particularly in the face of increased tension, clear aqueous veins were usually readily apparent.

Discussion

This work further demonstrates the inherent instability of the glaucomatous eye as compared to the normal, not only in the tension but also in the flow of aqueous humour.

Miotics temporarily increase the rate of flow, but in only 50 per cent. of the cases studied was there an associated fall in the tension. The remainder were about equally divided between those in which the tension remained unaltered and those showing a slight elevation. This shows that rate of flow and ocular tension (as measured by Schiötz tonometry) do not bear a constant relationship to one another. Moreover in seventeen of our cases there was a spontaneous drop in the concentration of fluorescein without tension change. This was usually a bilateral phenomenon. The degree of increased flow as indicated by a fall in concentration of fluorescein does not indicate the degree or direction of tension change in most cases. Similarly, signs of increased flow of clear fluid in aqueous veins, occurring as they do during periods of falling concentration of fluorescein, must not necessarily be taken as the index of tension change. In other words, changes in the flow of clear fluid in aqueous veins are related to rate of flow of aqueous humour, not necessarily to tension.

In conclusion, although a change in rate of bulk flow of aqueous humour is reflected in a change of flow in the aqueous veins, neither bears a constant parallel relationship to changes in tonometric readings. Although the rate of escape of aqueous humour from the anterior chamber through its exit channels is obviously important, the present findings indicate that it by no means explains all the changes found in tonometric readings and that a much broader concept must be envisaged, to include such factors as uveal tone, changes in scleral rigidity, and rate of formation of aqueous humour.

Summary

An improved method of measuring changes in the concentration of fluorescein in the anterior chamber without disrupting the physiological state of the human eye is described. In these experiments fluorescein was administered by the instillation method. Fluctuations in the bulk rate of flow, either spontaneous or after the instillation of miotics, were reflected in changes in flow of clear fluid in the aqueous veins, but neither the fluctuations nor changes in the aqueous veins bore a constant parallel relationship to the tonometric readings.

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Brit. J. Ophthal. (1953), **38**, 273.

OCULAR DISEASE DUE TO BRUCELLOSIS*

BY

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ALL the chronic granulomatous infections may occasionally give rise to ocular disease, and tuberculosis and syphilis are the best known in Great Britain. Brucellosis is an infection which should, at least in its chronic forms, be regarded as an important member of this group, and ought to be remembered as a possibility when the cause of certain eye diseases is being investigated.

Standard text-books on ophthalmology (e.g. Duke-Elder, 1949) make only small reference to brucellosis. References to ocular involvement in brucellosis are to be found in the American and European literature, but such cases do not seem to have been described in Great Britain. While the case to be reported cannot, therefore, be regarded as a rarity, it may draw attention to the desirability for fuller investigation in such cases than has been customary.

Survey of the Literature

Woods and Guyton (1944) studied two hundred cases of uveitis, and found serological evidence of brucellosis in fifteen. Cases of sarcoidosis also numbered fifteen; thus these two diseases were each responsible for 7½ per cent. of the total. As brucellosis frequently occurs without serological evidence, the true percentage could well have been higher than this. The cases comprised seven recurrent iritis, five generalized uveitis, and three cases choroiditis. One eye was sectioned after excision for phthisis bulbi, and showed "non-specific uveitis with several conspicuous lymphoid nodules, a picture quite suggestive of that of periodic ophthalmia of horses".† A case of nummular keratitis attributed to brucellosis outside this series was also mentioned.

Harris (1945) reported one case of recurrent keratitis and three of recurrent iritis probably due to brucellosis. In only one of these was the diagnosis confirmed serologically; the others had positive skin-tests and clinical signs to support the diagnosis of chronic brucellosis.

Kuzherskaya (1951) found one case of iridocyclitis, one of bilateral optic neuritis, and one of bilateral optic atrophy, among 101 cases of established brucellosis.

Pagliarani (1951) described four cases of melitensis infection in which ocular symptoms caused medical attention to be sought. These comprised two cases of exudative choroiditis, one of recurrent optic neuritis with left abducens paresis and one of lacrimal gland enlargement diagnosed as bilateral dacryoadenitis. He found in the literature over one hundred cases of brucellosis with ocular involvement during the course of the disease. Optic neuritis, uveitis, and retinal lesions

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†Horses are liable to contract brucellosis, as are all the ungulata.

were most frequently reported, and, less often, keratitis, palsies, and conjunctival and episcleral lesions.

Nelson-Jones (1952) gives a good general account of brucellosis in its many possible clinical forms in Great Britain.

Barrett and Rickards (1953) deal in detail with chronic brucellosis, with histological findings, and photographs of the granulomatous lesions in liver biopsies. The latter give surprising examples of chronicity in some of their cases; their diagnostic routine is an important contribution, and will be given below.

Present Observations

Symptoms.—These vary greatly in severity, and can simulate many other conditions. Leading questions are usually necessary and one should enquire after rheumatic pains or stiffness in the back, chest, or limbs; increased sweating, especially at night; readiness to fatigue; pain or swelling of knees, ankles, or other joints; headaches; chills or feverish bouts; gastro-intestinal symptoms, such as appetite and constipation.

Symptomatology often closely resembles that of the neuroses; one has heard, for example, of an airman with undiagnosed chronic brucellosis, who was boarded unfit on psychiatric grounds. Few patients with chronic brucellosis appear ill, even those with severe complaints; in some there are indeterminate complaints only, they are " run-down " and easily tired, and, in the absence of anything definite, an ophthalmic patient may have his eye-condition attributed to a non-specific infection in an unknown focus, when " all investigations prove negative " (an oft-recurring phrase with which we are only too familiar at clinical meetings). Severe symptoms occasionally simulate angina pectoris (probably due to sensory nerve involvement), warty lupus, rheumatic fever, rheumatoid arthritis, appendicitis, cholecystitis, sciatica, and lumbago. Three cases described by Barrett and Rickards had had viscera removed without benefit, on surgical diagnoses; one had recurrent haematuria, another recurrent haemoptysis, another typical asthma.

Signs.—These are usually few or absent. A slight enlargement of spleen and/or liver can be detected in most cases. Joints which are often painful and swollen may appear normal when examination is made. Bursitis can occur, and an excised bursa from a case of "housemaid's knee" has been reported to be of brucellar origin. Temperatures are only occasionally high.

Infection.—Milk is the source of most human infection, but veterinary and farm workers are liable to acquire the disease by other, direct, sources. In large towns pasteurized milk cannot cause infection, but on holiday (as in the Lake District) town-dwellers may run a definite risk from consuming raw milk. Man-to-man infection has not been reported. Pigs, horses, sheep, goats, and other ungulata form a natural reservoir of infection for cows and humans, a point not always appreciated.

Incidence.—Dalrymple-Champneys (1952) estimates that at least five hundred cases occur each year in Great Britain. He pointed out in 1953 that about 15 per cent. of cattle still harboured the infection as against some

40 per cent. before vaccines had been used. All milk, including tuberculin-tested, that has not been heat-treated is thus suspect. There may be a large number of cases which remain undetected, or wrongly diagnosed.

Pathology.—*Brucella melitensis* and *Br. suis* are rare in Great Britain where *Br. abortus* is usually the cause of the illness. All three strains may infect any of the cattle and live-stock mentioned above. *Br. suis* is not confined to pigs, and pigs can harbour the normally-bovine strain, for example. Two cows were found to harbour *Br. melitensis*, and Barrett and Rickards showed photomicrographs of the brucellar lesions of the liver after slaughter. *Br. abortus* is less virulent to man than either of the other strains. Bacteria ingested although phagocytosed may remain viable. Phagocytes containing brucellae are removed from the blood by cells of the reticuloendothelial system, and the organisms thereby establish themselves intracellularly in liver, spleen, and red marrow. Toxins and occasional showers of free organisms are responsible for relapses and recurrent symptoms of ill-health. An affinity for serous membranes sometimes exists, and organisms may settle in the pia-arachnoid, endocardium, chorion, pleura, etc. Neurological involvement has been reported, and in ophthalmology we must note ocular palsies as a possible occurrence in brucellosis. Apart from local lesions there may be allergic manifestations such as bronchial asthma, synovial oedema, and vasomotor upsets. A hypersensitivity to culture-filtrates can nearly always be shown by intradermal testing. Antibodies are often non-demonstrable in chronic cases unless specially stimulated by vaccines, etc. Liver-biopsy specimens show granulomata 100 to 180μ in diameter, not related to the portal tracts or specific zones of the lobule, consisting largely of epithelioid cells and sometimes giant-cells, rather similar to lesions of sarcoidosis and to non-caseating miliary tubercles. Focal lymphocytic infiltration also occurs. Bacteria are not seen in the lesions. An eye sectioned for brucellar involvement showed lymphoid infiltration of the blood-vessels (Pagliarani, 1951), and another eye showed lymphocytic nodules in the diseased choroid.

Diagnosis

Blood Cultures.—These are positive only at times, and practically only in acute cases or in febrile attacks in chronic cases. Negative cultures are, therefore, of no diagnostic significance.

Serological Tests.—Agglutination tests are preferred, but these are negative in many cases. Barrett and Rickards found negative results or titres below 1:100 in half their cases. One case gave 1:15,000. In patients with symptoms titres over 1:120 can usually be taken as practically diagnostic, but negative results do not exclude the conditions.

Intradermal Brucellin Test.—This gives presumptive evidence of brucellosis, but does not definitely prove that there is active infection. Barrett and Rickards have disproved the claim by Spink and others (1952) that the skin-test

is of little value; they show that when the skin-test is positive, and a low serum-agglutinin titre is found, a high titre on repetition 2 weeks after the skin-test is *diagnostic* of active brucellosis (*e.g.*, low initial titres rose 4-fold to 8-fold 2 weeks after the skin-test; zero titres rose to 1:60 or even to 1:640). The odd case which did not conform to this had symptoms of extreme chronicity, and a liver biopsy gave significant findings. Healthy volunteers who had repeated intradermal " tests " never gave titres exceeding 1:80 at any time during the experiment.

Hepatic Biopsy.—This is not a formidable procedure, and may give valuable evidence of the disease in difficult cases.

Routine Diagnostic Procedure in Doubtful Cases.—Perform skin-test on one arm with 0·1 ml. brucellin and take blood for W.R. etc., and for brucella-titre. (A tuberculin test can be done on the other arm at the same time using a separate syringe.) Observe two days later. If erythema with oedema is found, 2–6 cm. in diameter, the skin-test is positive, and a further sample of blood should be taken for agglutinin-titre two weeks after the first. A sharp rise, as indicated above, is diagnostic. If doubt remains, a healthy portion of liver obtained at biopsy will rule out, with sufficient certainty, the possibility of brucellosis.

Treatment.—The case reported below had the recommended treatment, though some authorities use pyrexial therapy, specific vaccines, or sulphadiazine in conjunction with it. Relapses are the rule with shorter courses of antibiotics. Further advances in treatment are necessary before brucellosis can be regarded as a curable disease in every case. Early enthusiastic reports of cure, such as those quoted in bulletins circularized by firms dealing in antibiotics, have not taken into account the high relapse rate found a few months after apparent cure.

Biggam (1953) suggests short monthly courses of aureomycin or terramycin for relapses, to assist the natural defences of the body in what is a self-limiting disease though with a natural duration of many years in some cases.

Case Report

A man aged 33 years attended the out-patients' department on November 13, 1952, complaining of impaired vision in the right eye. This had first been noticed about 2 months before, but had been much worse for the last 4 days.

Examination.—Visual acuity was 6/36 in the right eye and 6/9 in the left. The right pupil was slightly less active to light than the left. The tension was not raised. The right eye was slightly irritable and congested. Slit-lamp examination of the right eye showed an aqueous flare, and a few fine keratic precipitates. The left eye was normal in appearance. Fundus examination of the right eye showed hazy vitreous, and small patches of anterior choroiditis.

Diagnosis.—Subacute anterior uveitis of the right eye.

Laboratory Investigations.—Wasserman reaction, Kahn, G.C.F.T. negative. *X* rays revealed nothing unusual in chest, sinuses, and teeth.

Mantoux test 1:10,000—weak positive.

Brucellin intradermal test, 0·1 ml., strongly positive.

Through an oversight, the blood for brucella-agglutination was not collected until 2 weeks after the skin-test, and the titre then found was 1:120.

History.—In view of this evidence of brucellosis, a careful history was taken to seek confirmation of this diagnosis. The patient was not of a complaining disposition, and leading questions were necessary. He was a fish-dock worker by trade. He had had malaria in 1942–43, with no recurrence. He left the Mediterranean area in 1944, and had enjoyed excellent health until he had a bilious sickness for 6 weeks in November, 1949. Since then, night-sweats, constipation, headaches, and early fatigue had persisted. For 2 or 3 years he had had a very " blotchy " skin-condition of the face and neck, with flushing of the face at times. In 1951 he had phlebitis of both legs, and painful spontaneous " bruises " of the arms and legs lasting about 3 days. For the last year his ankles had been swelling from time to time. He was fond of drinking milk, but his home supply was pasteurized.

Course of Eye-Condition.—By December 18, 1952, visual acuity was 6/12 in the right eye. Vitreous haze was still present, but the choroidal lesions were not apparently active. The keratic precipitates cleared apart from a few small pigment-spots. Treatment with atropine was stopped and the patient was kept under observation. He was not anxious to have treatment for brucellosis as his eye had improved.

Involvement of Other Eye.—On January 8, 1953, the left eye (not previously affected) was found to have developed an acute periphlebitis of superior temporal retinal veins. The right eye was now quiet. Visual acuity in the left eye was 6/36, with hazy vitreous, and a dilated, tortuous superior temporal vein was seen, its peripheral tributaries obliterated by white sheathing. At the arterio-venous crossing nearest to the disc the vein was nipped severely by pressure due to oedema in the vascular sheath. Small petechial haemorrhages were present in this quadrant of the retina. One small exudate was seen near the superior nasal vein.

Treatment.—Chloromycetin 0·75 g. was given 6-hrly, and admission to hospital arranged for the following day. The antibiotic was continued for 9 more days. For the next 21 days he was given aureomycin 2·5 g./day, and intramuscular dihydrostreptomycin 1g. 12-hrly. He also received massive doses of vitamin B-complex and vitamin C. (His body weight was 12 stone). Response to treatment was first evident in his complexion, which cleared remarkably, and phlebitic patches in the thigh muscles then cleared. The left eye showed no spread of the disease to other quadrants, and the small exudate near the superior nasal vein cleared. Complete occlusion of the affected vein and its tributaries developed, but the inflammatory vitreous haze was gone within 2 weeks. The liver was slightly enlarged at the beginning of treatment, and the thymol turbidity was reported as 4·2 units. The Van den Bergh reactions were negative. After treatment the thymol turbidity had improved to 2·5 units on March 11, 1953. The *Brucella* antibody titre fell rapidly to zero during treatment. Attempts to stimulate antibodies, in the hope of preventing relapse, were made by giving repeated doses of brucellin every week for 7 weeks, starting in the last week of treatment, but the titre persisted at zero despite this treatment.

Final Result.—Obvious signs of systemic relapse appeared towards the end of March. The patient attended no further, and failed to keep his appointments until June 4, 1953, when the ocular condition was found to be quiet. Visual acuity was 6/9 in the right eye and 6/18 in the left. Apart from a floating opacity, the right eye was satisfactory; the left eye had developed a low-grade iritis since the last attendance, but was now quiet, with a number of posterior synechiae remaining. The left disc was pale, and the superior temporal quadrant of the retina was avascular and atrophic.

The patient's general health had improved, and he was working and free from symptoms of active infection. Spectacles were prescribed, and he has not attended since.

Summary

Chronic brucellosis is described as one of the infective granulomatous diseases which may have ocular complications in a small proportion of cases.

The literature referring to ophthalmic brucellosis is briefly reviewed, the clinical features of chronic brucellosis are outlined, and a short account of its pathology is given, including histological findings of the almost invariable hepatic lesions disclosed by biopsy.

An improved diagnostic routine for brucellosis is described, which might well be included whenever investigations for syphilis, tuberculosis, etc., are undertaken.

A case is reported of a patient with an anterior uveitis in one eye, later followed by periphlebitis retinae in the other eye. He gave a typical history of chronic brucellosis and responded to antibiotic therapy.

It is concluded that the frequency of chronic brucellosis as a cause of uveitis and other ocular diseases will not be known in Great Britain until ophthalmologists include skin tests and blood-agglutination tests for brucellosis in their list of routine investigations.

I am indebted to Lt.-Col. H. J. Bensted, of the Central Public Health Laboratory, Colindale Avenue, London, N.W.9, for a supply of brucellin antigen for skin-testing.

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EQUATORIAL CATARACT AFTER CORNEO-SCLERAL TREPHINING*

BY

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THE occurrence of cataract in association with glaucoma presents a therapeutic problem of some magnitude which has attracted a good deal of attention in recent years (Samuels, 1947; Sourdille, 1950; Chandler, 1949; François, 1947; Williamson-Noble, 1953). The difficulties of treatment are not made less by the uncertainty which still exists as to the role played by the glaucomatous process and its treatment in the genesis of the lens opacity.

Since the utility of corneo-scleral trephining was first established after its introduction by Elliot in the early 20th century, the cause of the cataract which may be seen post-operatively in some cases has been a subject of speculation. Elliot (1914) was not convinced that the cataract was due to the operative interference, and although, as experience with the operation has become world-wide, the contrary view has found its advocates, the general opinion appears still to be in agreement with his, provided that direct operative damage to the lens has not taken place (Duke-Elder, 1940; Spaeth, 1941; Arruga, 1952). The association of delayed reformation of the anterior chamber with post-trephine cataract is, however, generally familiar, and this post-operative complication has been assigned a major place in the causation of the lens opacity by Duke-Elder (1940) and by Williamson-Noble (1953).

The purpose of this paper is to present four cases which showed lens changes after trephining, and in which the clinical features can be fairly clearly interpreted in the light of the gonioscopic picture of the site of the operation. This distinguishes them as a type of post-trephine cataract not previously described, and permits the formulation of a possible hypothesis to account for them.

Case Reports

Case 1, female, aged 69, was admitted to Moorfields on April 27, 1939, with an acute attack of congestive glaucoma which responded in some degree to medical treatment; although the tension remained high, visual acuity was 6/9; the eye (left) was trephined on May 1, 1939, and the post-operative course appears to have been uneventful.

During the succeeding years vision in the left eye gradually failed, and, when she was first examined at the Institute of Ophthalmology on July 12, 1949, was 6/18 with a correction of $-1{\cdot}0/-3{\cdot}5$ axis 90°. Marked cupping of the disc was noted and the visual field showed peripheral constriction.

The gonioscopic appearance of the operation area at that time showed a basal iridectomy flanked by corneal peripheral anterior synechiae (Fig. 1, overleaf). The trephine was well-sited on the limbus; but was largely filled by a tube of opacifying lens capsule which could

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FIG. 1.—Case 1, 10¼ years after operation (May 24, 1950).

FIG. 2.—Case 1, 3 years later (June 19, 1953).

be seen to be herniated from the equator of the lens opposite the trephine aperture.*

Since that time an equatorial lens opacity has been seen to form and to extend to the central area of the lens with a coincident reduction in vision to finger-counting (June 17, 1953). Examination with the gonioscope now shows the structures of the angle in the same relation to one another; but the tube of lens capsule seen in 1949 now appears to extend from the cataract into the trephine-hole as a flat, opaque, white band with a dense nodule of opacity at its base (Fig. 2) upon the equator of the lens.

Case 2, female, aged 61, was admitted to Moorfields with an acute attack of congestive glaucoma. The eye was trephined with complete iridectomy on March 6, 1944.

The immediate post-operative course called forth no comment; but the ocular tension was noted to be low. When she was first examined at the Institute on May 11, 1951, the trephine bleb was draining well, the tension was normal, the disc deeply cupped, and vision down to finger-counting with the field reduced to a minute paracentral island.

The gonioscopic appearance of the operation area showed a complete iridectomy with the trephine well-sited on the trabeculae. The trephine aperture, however, was seen to be behind a strand of lens capsule which was adherent to its anterior lip (Fig. 3).

When the patient was last examined (June 24, 1953) the gonioscopic appearances were substantially unaltered; but a small equatorial cataract was apparent beneath the capsule, and the opacity was evidently spreading towards the pupillary area.

Case 3, male, aged 75, was admitted to Moorfields after 2 years on miotics for minor congestive attacks of glaucoma and with a pre-operative tension of 41 mm. Hg Schiötz in both eyes. The right eye was trephined on May 11, 1951, and the left on June 27, 1951.

Post-operative examination at the first dressing showed a total hyphaema in the left eye, and when, during the next 2 weeks, it cleared, large choroidal detachments and iridodialyses were visible. The detachments were seen to subside during the following 4 weeks.

*This case is referred to in the Discussion on Gonioscopy at the Royal Society of Medicine (Hobbs, 1950).

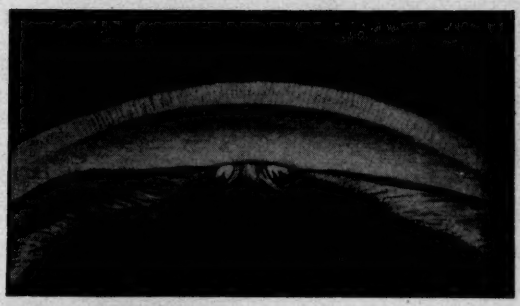

FIG. 3.—Case 2, 7 years after operation (May 11, 1951).

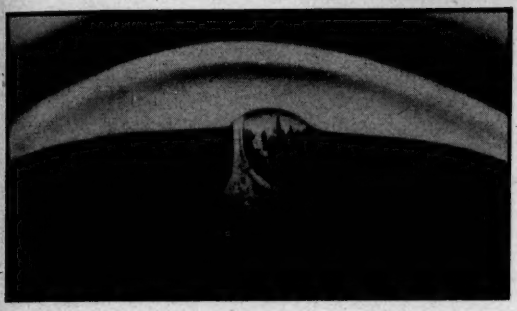

FIG. 4.—Case 4 (August 31, 1953).

Reformation of the anterior chamber in the right eye was slow, and a large choroidal detachment was early apparent which subsided during the first post-operative month.

When the patient was first examined at the Institute (April 10, 1953), the right bleb indicated good drainage, but vision in this eye was reduced to finger-counting; in the left eye it was 4/60, and in both there were extensive central and peripheral field loss. Tension in the right eye was 20 mm. and in the left 30 mm. Hg Schiötz.

The gonioscopic appearance of the operation areas showed, in the right eye, the trephine well-sited on the trabeculae and patent. Into it there passed a strip of transparent tissue (? zonule) which was attached to the equator of the lens. In the left eye, also, the trephine was well-sited on the trabeculae, and was patent, but partly obscured by an adhesion of the lens capsule to its antero-nasal edge.

Case 4, male, aged 72, was admitted to Moorfields with a history of visual deterioration in the left eye for 2 months, and showed signs of typical chronic simple glaucoma without congestive attacks. The tension (digitally) was "full". The eye was trephined on May 29, 1945.

The post-operative course was uneventful; but a week after operation the anterior chamber remained shallow. Subsequently the vision in this eye gradually deteriorated so that when the patient was examined at the Institute of Ophthalmology (August 31, 1953), it was reduced to finger-counting. The trephine at this time was draining well; but a maturing cataract obscured any view of the fundus.

The gonioscopic appearance of the operation area (Fig. 4) showed the trephine hole anterior to the ciliary body, but with a prolapsed ciliary process passing into it. An opaque strand of lens capsule was seen to adhere to the antero-nasal edge of the fistula.

Discussion

The common features of these four cases which we should like to emphasize are, first, the capsular adhesion to the operation site; second, the presence

of a history of congestive attacks, amounting to an attack of acute congestive glaucoma which immediately preceded operation in two of them; third, the occurrence of delayed reformation of the anterior chamber with choroidal detachments in one of them.

Capsular Adhesion.—Adhesions of this sort were first noted by Sugar (1941); but no cataract had been seen at the time of his report. The occurrence of a localized equatorial cataract in the first two cases might, at first sight, be taken to indicate that the condition was the result of direct operative trauma to the lens; but the fact that the opacities have formed slowly (over a period of some 10 years in Case 1, and 9 years in Case 2) suggests to us that they are less likely to have arisen in this way than to have resulted from the prolonged tension on the lens capsule. Very little opacity was present in Case 1 10 years after operation, and none in Case 2 after 7 years, although in both an equatorial cataract has been seen to develop subsequently during the period of observation, and has spread in the first case to involve the central part of the lens. In Case 4 no equatorial opacity has been seen; but the cataract, 8 years after operation, remains immature and is denser in its upper part. In Case 3, operated upon more recently, the lens remains clear. Such opacities are in marked contrast with the rapidly-forming traumatic cataract which is generally accepted to be the result of direct injury of the lens—a process which is said to be exaggerated when the eye is glaucomatous (Samuels, 1947) and occasionally to present an acute post-operative disaster. Indeed, Verhoeff (1918) reported that the majority of eyes for which enucleation was necessary as the result of complications following trephining had suffered injury to the lens.

The cause of the capsular adhesion hence becomes of considerable importance; and it may be recalled that one of us (H.E.H.), in a reference to Case 1 in 1950, suggested that the appearances might be interpreted as resulting primarily from prolapse into the trephine-hole of ciliary processes, which subsequently, by tension on the suspensory ligament, drew a tent of lens capsule after them. Such prolapse of the ciliary processes is a not uncommon finding with the gonioscope after trephining (Sugar, 1942; Troncoso, 1948), but it usually occurs when the trephine aperture is to some extent retroplaced. In all of our cases the trephine-hole is sited anteriorly over the trabeculae, and, since, in the only one of them in which a prolapsed ciliary process is seen (Case 4), this is quite separate from the lens capsule, the proffered explanation must remain entirely hypothetical. On the other hand, it is noteworthy that, in the three last cases the lens capsule does not pass through the trephine-hole, but is adherent to its *anterior* lip. This, it seems to us, suggests that the lens itself must at some time, and most probably at the time of operation, have become subluxated upward and tilted forward toward the new aqueous exit at the trephine aperture. The tendency for forward displacement of the lens to occur in congestive glaucoma is well known, and has been responsible, after iridectomy during an acute attack, for the severe and intractable recurrence of hypertension, to which von Graefe gave the name of " malignant glaucoma ". This condition has recently been reviewed by Chandler (1950).

Pressure in the vitreous chamber, uncompensated in the anterior chamber, has appeared to be the most likely explanation of this condition, and has been attributed to swelling of the vitreous (Reese, 1950), or uveal congestion (Chandler, 1950). Whatever the immediate cause, however, the end-result is the same, namely, a

great and rapidly produced disparity between the pressures in the anterior and vitreous chambers, with a tendency for the lens-zonule diaphragm to be forced forward towards the point of reduced pressure at the site of the incision.

The adhesion of lens capsule at the operation site in the cases described above, suggests that as well as this forward movement, there is a subluxation upward which brings the lens into contact with the trephine aperture. Such a movement would presumably be determined by the aqueous escaping as the surgical fistula is made, and a similar mechanism, in a more pronounced degree, has apparently been active in a case of malignant glaucoma recently seen by one of us (R.S.), of which a section of the subsequently excised eye is shown in Fig. 5.

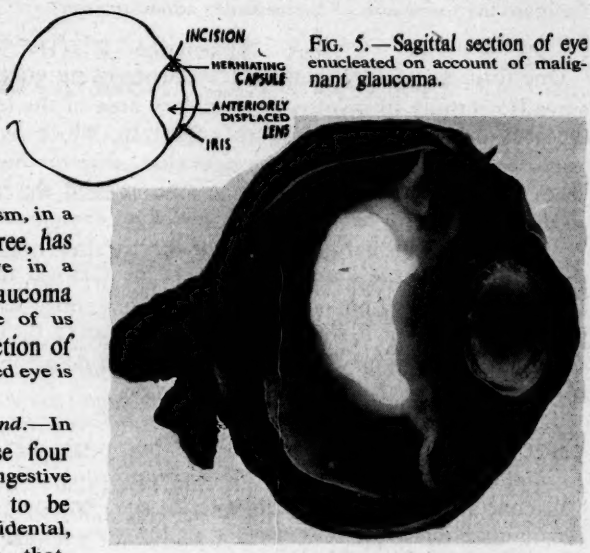

FIG. 5.—Sagittal section of eye enucleated on account of malignant glaucoma.

Congestive Background.—In at least two of these four cases, therefore, the congestive background appears to be rather more than coincidental, and it seems likely that, whether or not the measurable tension was severely raised at the time of operation, a considerable forward thrust must have been exerted upon the lens diaphragm in order to bring the equator of the lens as far forward as the anterior lip of an anteriorly placed trephine. The congestion in the uveal tract behind the lens in an acute congestive attack is an obvious source of such pressure, and it seems reasonable to hold it responsible in the two cases in which an acute attack immediately preceded operation.

It seems likely from these considerations, therefore, that this complication arises from a relative excess of pressure in the vitreous chamber over that in the anterior chamber. Pre-operative uveal congestion may, of course, have been present as the primary cause of the ocular hypertension, and may have been accentuated by the fall in anterior chamber pressure when aqueous was allowed to escape through the wound; or the escape of aqueous alone, if sufficiently rapid, may have been responsible for the disproportion.

Delayed Re-Formation of the Anterior Chamber and Choroidal Detachment.—The association of post-trephine cataract with delayed reformation of the anterior chamber has already been referred to above, and, although no satisfactory explanation of it has yet been offered, the fact that, in Case 3, choroidal detachments were also present is of additional and relevant interest. After cataract extraction or trephining, such detachments are well known to be associated with hypotony and with a shallow anterior chamber, and although the mechanism by which they

arise may differ somewhat in the two types of case, it seems certain that they can only appear when, in the presence of lowered ocular tension, fluid passes into the subchoroidal space. Such a condition, in this case, by adding to the retrolenticular volume, could provide in the vitreous chamber the thrust needed to retain the lens diaphragm in its forward position during the early post-operative period, and so to facilitate the formation of the capsular adhesion seen.

Conclusion

One form of post-trephine cataract arises as an equatorial opacity which spreads centrally to involve the pupillary area of the lens. An adhesion of the lens capsule to the trephine aperture, which is best demonstrated gonioscopally, appears to be its immediate determining cause. Of the four cases reported in which such an adhesion is present, the cataract has developed in three, the fourth having been operated on comparatively recently.

The adhesion probably forms at, or shortly after, operation, when, through the emptying of the anterior chamber, the forward thrust of the pressure behind the lens is unopposed. Pre-operative congestion and post-operative choroidal detachment with delayed reformation of the anterior chamber are, therefore, likely to play a part in causing, and maintaining, the displacement of the lens.

It seems desirable, therefore, that when a fistulizing operation is contemplated in the presence of high tension, appropriate measures should be taken to minimize the abruptness of the decompression. Some of these measures will concern the actual operative technique; but such medical measures as retrobulbar injection of novocaine or intravenous injection of sorbitol, or alternatively preliminary posterior sclerotomy, should tend to diminish the strain on the lens-zonule-diaphragm at operation by reducing the ocular tension as a whole. The findings in trephined eyes first prompted this suggestion, but it seems likely that the same considerations apply to such other decompression operations as iris inclusion and cyclodialysis, which are by no means free from the complication of post-operative cataract.

We should like to record our appreciation of the excellence of the gonioscopy paintings which are the work of Mr. T. Tarrant, and our indebtedness to Miss E. J. Brown for invaluable secretarial assistance.

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Brit. J. Ophthal. (1954) **38**, 285.

PRIMARY TUMOURS OF THE OPTIC NERVE IN VON RECKLINGHAUSEN'S DISEASE*

BY

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Rotterdam

THE ophthalmological symptoms of von Recklinghausen's syndrome are numerous. Multiple tumours of the superficial nerves may cause a plexiform neurofibromatosis, preferably situated in the superior eyelid and the region around the orbit. The intra-orbital and the ciliary nerves can also be affected. Defects in the bony orbital wall may cause a pulsating exophthalmos, and phakomata in the iris and congenital uveal ectropion may be present. Van der Hoeve (1932) was the first to describe tumours in the retina. An excellent study by Davis (1940) made it clear, however, that primary tumours of the optic nerve are probably the most important sign of von Recklinghausen's disease for the ophthalmologist. This view is also emphasized by the study of Bürki (1944) and the report of Offret (1951).

As the close relation between primary tumours of the optic nerve and von Recklinghausen's disease has not yet become generally known, it seems worth while to report the findings in two children of one family, both of whom showed the peripheral signs of von Recklinghausen's disease, and had a tumour in the optic nerve and the chiasm.

Case Reports

Case 1, a boy born on February 24, 1940, was seen for the first time in August, 1951. He was mentally defective and at that time it was not possible to determine the visual acuity. The right eye showed a myopic astigmatism of 2 dioptres; the left eye was emmetropic. The right eye showed a sursumvergent strabismus. The optic disc in both eyes was normal. The mother returned with the child in December, 1951, and stated that the function of the eyes had decreased during the last months. This time it was possible to determine the visual acuity, which was less than 1/10 in the right eye, and 4/10 in the left eye. The nerve head of the right eye was normal; the left eye showed a pale disc. No exophthalmos was present. It was supposed that the insufficient functioning of the right eye was to be considered as an amblyopia ex anopsia due to the myopic astigmatism, and that the visual acuity of the left eye had decreased by some pathological process in the left optic nerve. The boy was admitted to the municipal neurological hospital (B.G. Ziedses des Plantes).

Examination.—The following characteristics were noted:

(1) Marked mental defect;

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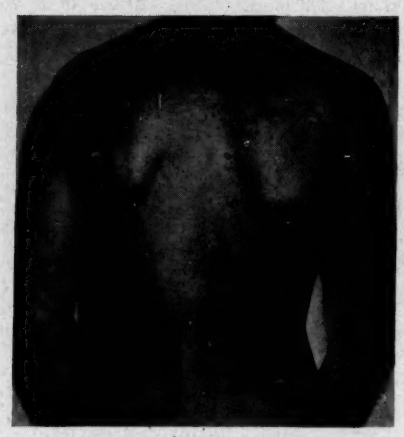

FIG. 1.—Case 1, *café-au-lait* pigmented patches.

(2) Many *café-au-lait* pigmented patches in the skin (Fig. 1); gooseflesh on the trunk and legs, and multiple pin-head fibromata on the right hip.

(3) Supra-symphyseal intra-abdominal tumour the size of a coconut;

(4) *X* rays showed no abnormal changes in the cranial bones, a minor enlargement of the right optic foramen (Fig. 2), and a marked enlargement of the left (Fig. 3). Ventriculograms could not be produced as it was impossible to fill the ventricles with air by the occipital route. The cerebral spinal fluid was normal. Laboratory examinations revealed no abnormalities.

(5) Ophthalmological examination during February, 1953, in the ophthalmic hospital (H. J. Flieringa), revealed that vitreous opacities had appeared in the right eye. The optic disc still showed a normal colour but a balloon-shaped retinal detachment had occurred in the temporal part of the fundus. Scattered retinal haemorrhages were visible on the detached retina and it seemed probable that a subretinal tumour had developed. The fundus of the left eye showed marked pallor of the disc without other anomalies. The visual field was concentrically narrowed seriously in the right eye and slightly in the left. The electroretinogram was absent in the right eye and normal in the left eye.

FIG. 2.—Case 1, minor enlargement of right optic foramen.

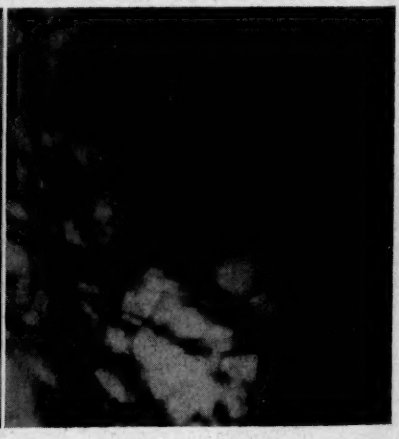

FIG. 3.—Case 1, marked enlargement of left optic foramen.

Operation.—On March 10, 1953, the left optic nerve and the chiasm were exposed by means of a left transfrontal craniotomy (M. P. A. M. De Grood) and a tumour of the left optic nerve and the chiasm was found. No specimen was removed for histological examination as the surgeon was convinced that a glioma of the left optic nerve and the chiasm was present.

Re-examination on July 3, 1953, revealed a slight papilloedema of the right eye. A large detachment of the retina with recent haemorrhages was visible in the lower temporal part of the fundus. It was clear that a growing subretinal tumour was present in this eye.

Case 2, sister of Case 1, born on February 15, 1945, who had been treated by another ophthalmologist since 1948, was first seen in October, 1950. A paralytic right abducens nerve was present; the right eye was amblyopic. The visual acuity of the left eye was 5/5. Both eyes were 3 dioptres hypermetropic. In December, 1951, the visual acuity of the

left eye was still 5/5. The mother came back with the girl in February, 1953, and said that after the Christmas holidays her teacher had complained that her writing had suddenly become very untidy. The visual acuity of the left eye had decreased to 1/10, but the fundus showed no abnormalities. The fundus of the right eye showed a pallor of the nervehead.

The girl was immediately sent to the same neurological hospital as her brother.

Examination.—The following characteristics were noted:

(1) No mental defect;

(2) Large *café-au-lait* pigmented patches on the trunk (Fig. 4). Cutaneous fibromata not present;

(3) *X* rays of the skull showed no anomalies; the optic foramina were of a somewhat triangular shape but were not enlarged. All the ventricles appeared too narrow, and the inferior anterior part of the third ventricle was not sufficiently filled with air. The tension of the cerebrospinal fluid was normal; it contained 9 lymphocytes in 3 cu. mm. and 0·091 per cent. albumen. The reactions of Nonne and Pandy were both positive; the colloid reactions were about normal.

Operation.—On March 18, 1953, the optic nerves and chiasm were exposed by a right transfrontal craniotomy (M. P. A. M. De Grood). The right optic nerve was white and thin, and emerged half a centimetre behind the optic foramen into a greyish-coloured tumour that could not be separated from the nerve. The chiasm was covered by the same grey tissue. The left optic nerve was also white and thin. A small piece of the tumour was excised for histological examination; a glioma of the right optic nerve and the chiasm was present (M. Straub).

Re-examination on July 3, 1953, revealed that the visual acuity of both eyes was about 1/60. The nervehead of the right eye was atrophic; the left optic disc showed slight temporal pallor.

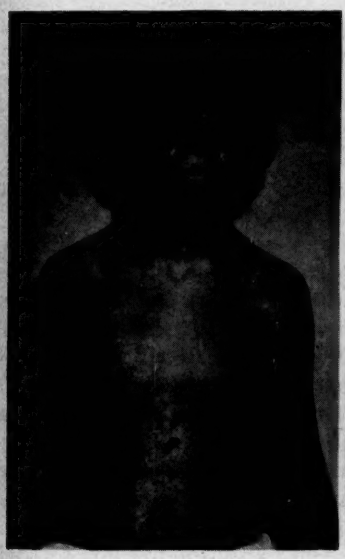

FIG. 4.—Case 2, younger sister of Case 1, *café-au-lait* pigmented patches.

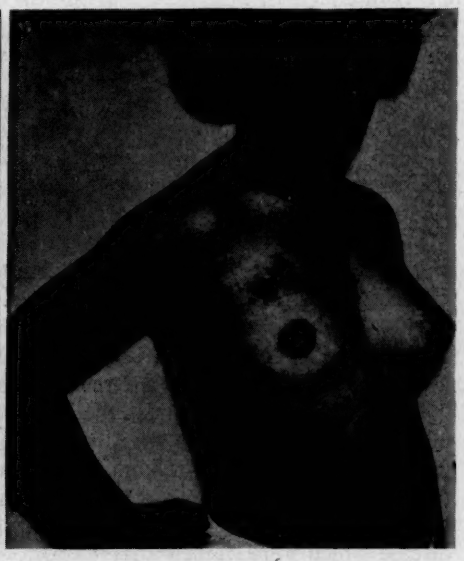

FIG. 5.—Twin-sister of Case 1, *café-au-lait* pigmented patches on trunk.

The family history showed that Case 1 was one of a pair of twins; his twin sister also showed serious mental deficiency, and numerous *café-au-lait* pigmented patches were visible on the trunk (Fig. 5). Her right eye was amblyopic with a myopia of 20 dioptres. The visual acuity of the left eye was 5/5; this eye was half a dioptre hypermetropic. Both the nerveheads appeared normal, and no anomalies were seen in the fundus except for a myopic atrophy in the right eye.

There were no other children. The father showed no signs of von Recklinghausen's disease, but the mother had many cutaneous fibromata and *café-au-lait*

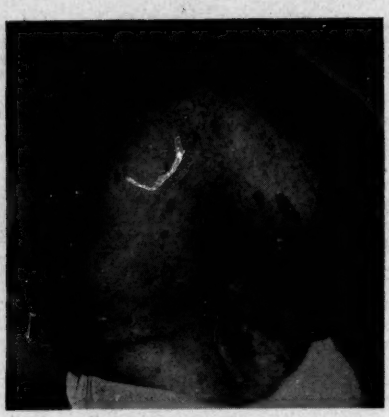

FIG. 6.—Mother of the three children, *café-au-lait* pigmented patches and cutaneous fibromata.

pigmented patches all over the whole body (Fig. 6). Both her eyes were normal.

Comment

It is not our purpose to discuss in detail the histology of the primary tumours of the optic nerve in von Recklinghausen's disease. Comprehensive studies have been made by Davis (1940), Bürki (1944), and Offret (1951). In the older literature the terminology is confused: glioma, gliosarcoma, fibroma, fibrosarcoma, neuroma, endothelioma, meningioma, fibromatosis, sarcoma, myxosarcoma, and so on, but Verhoeff (1922), Lundberg (1935), and Davis (1940) have classified them as:

(1) Tumours of the nerve: *gliomata*,
(2) Tumours of the sheaths: *meningiomata* or *endotheliomata*.

In addition to these two types some cases form a third category designated by Hudson (1912) as *fibromatosis*. Posner and Horrax (1948) were the last to publish such a case. Bürki may be right when he uses the names: *tumour-like fibrogliomatosis* and *neurofibrogliomatosis*, but he may cause fresh confusion in the nomenclature of tumours of the optic nerve.

Most of such tumours, especially in children, originate within the nerves, and are gliomata. A totally different structure is seen in a few tumours in older people, which have the characteristics of endotheliomata or meningiomata. Classification by age of patient is rather risky, as Saebø (1949) described a glioma in a patient aged 43 years, and François and Rabaey (1952) described a meningioma in a 5-year-old child.

Davis was the first to stress the close relation between primary tumours of the optic nerve and von Recklinghausen's disease. He found 24 anatomically studied cases in the literature; twenty gliomata and four endotheliomata; his own five cases were also gliomata. Bürki afterwards published two other cases of gliomata of the optic nerve in von Recklinghausen's disease which were studied anatomically. Our two cases, diagnosed during operation, make a total of 29 gliomata against four endotheliomata.

Bürki found that 12·3 per cent. of 430 cases of tumour of the optic nerve showed a general neurofibromatosis, but this percentage has risen to 37·6 per cent. in 93 cases since 1933. Many cases of von Recklinghausen's disease still remain unnoticed as the ophthalmologist's attention is fixed on the ocular lesion and he often overlooks the associated changes in the other parts of the body, as in the five cases of Davis, both patients of Bürki, and our own two patients. The mild general manifestations of von Recklinghausen's disease,

especially the *café-au-lait* pigmented patches on the skin, are so important for the recognition of the true nature of the eye disease, that ophthalmologists should carefully examine every child with unilateral amblyopia for these patches. One may conclude with Bürki that a tumour of the optic nerve is often a phenomenon of von Recklinghausen's disease, and that a solitary tumour of the optic nerve may be the first or only symptom of it.

Gliomata of the chiasm also often are found in von Recklinghausen's disease. Cushing (1930) found symptoms of this disease in six of eighteen patients with the chiasmal syndrome of primary optic atrophy and bilateral field defects in adults with normal sella turcica.

The youth of most patients with a glioma of the optic nerve indicates that the lesion may be congenital in origin. Reese (1951) stated that 60–75 per cent. of all tumours of the optic nerves are encountered in children in the first ten years of life. Davis reported that nineteen of 36 patients with a primary tumour of the optic nerve in von Recklinghausen's disease were under 13 years of age.

This disease has a marked hereditary tendency, and many familial and hereditary histories are given in the literature (Waardenburg, 1932), but familial cases of primary tumour of the optic nerve in this disease are rare. Two of the patients reported by Davis were brother and sister, and Holmström (1928) described two sisters, aged 4 and 5 years, who both showed exophthalmos, reduced visual acuity, and a markedly enlarged optic foramen of the right eye. Cases 1 and 2 above are the third pair of siblings with a primary tumour of the optic nerve in von Recklinghausen's disease.

Summary

Clinical reports are given of two children of one family both with a glioma of the optic nerve and the chiasm. Both the children, the twin of one of them, and their mother, showed generalized symptoms of von Recklinghausen's disease. Tumours of the optic nerve and the chiasm are relatively frequent in von Recklinghausen's disease; most of the tumours are gliomata and some are endotheliomata.

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EVALUATION OF THE WATER-DRINKING TEST*†

BY

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DIFFERENT degrees of reliability of the water-drinking test for glaucoma have been reported in the literature. This may partly be explained by the fact that an insufficient number of tests have been carried out on healthy subjects, so that the physiological limits of the response to the test were not clear. Furthermore, the incidence of positive results in glaucomatous eyes with a normal initial tension has generally not been kept apart from those found in eyes with initially high tension. Both criticisms apply to an earlier paper in this Journal (Leydhecker, 1950), and the present re-consideration of the subject has been stimulated by the work of Agarwal and Sharma (1953), in which similar errors seem to be contained.

Previous Investigations

(*A*) *Effect of the Test on Normal Eyes.*—Decker (1929) examined fifteen subjects and found no rise of tension above the limits of error of tonometry. Poos (1930) saw " in many cases " rises of 5 or 8 mm. Hg Schiötz. Wegner (1930) mentioned rises of "several" mm. Hg. Heegaard and Larsen (1931) obtained maximal rises of 4 mm. Hg. Ohm (1936) gave the increase of tension as a percentage of the initial tension so that his results are difficult to compare. Meves (1940) injected pituitary hormone (hypophysin), in addition to the ingestion of 1,000 ml. water, and observed a maximal rise of tension of 8 mm. Hg Schiötz in six healthy eyes. Sugar (1948) who was the first to do a large number of tests on healthy subjects, found in 143 eyes a maximal rise of 9 mm. Hg or a ceiling of 32 mm. Hg. Honigmund (1951) examined seventy eyes of non-glaucomatous subjects after the ingestion of 1,000 ml. water; in vegetative dystonia she observed rises of 10 or even 12 mm. Hg Schiötz in four eyes. Rohrschneider (1952) examined forty healthy students: in 30 per cent rises of 6 to 12 mm. Hg occurred, in six cases the ceiling was 30 or 32 mm. Hg, in three the rise was 10 mm. Hg, and in one 12 mm. Hg. Agarwal and Sharma (1953) obtained rises of 2 to 6 mm. Hg in fifty healthy eyes, but in one considered to be pre-glaucomatous a rise of 10 mm. Hg occurred.

(*B*) *Incidence of Pathological Results in Glaucomatous Eyes.*—The results of Schmidt (1929, 1931), Wegner (1930), Ohm (1936), and Sugar (1948) are difficult to evaluate, since the increase of tension in their cases is not fully stated. Majorova and Glinika (1939) did 44 tests on 23 patients and obtained a rise of 6 mm. Hg Schiötz or more in four out of twelve eyes. Bloomfield and Kellermann (1947) observed rises of 10 mm. Hg or more in twelve out of 22 eyes with simple glaucoma. Schmidt (1950) reported a ceiling of 30 mm. Hg or more in 60·8 per cent of 250 glaucomatous eyes; amongst 33 tension curves of glaucomatous eyes with an initial tension below 30 mm. Hg there were eight with rises of 10 mm. Hg or more. Sugar (1948, 1951) observed rises of over 9 mm. Hg in 44 per cent. of 112 unoperated eyes with simple glaucoma; he points out (1951) that " with increasing levels of initial tension

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†Most of these experiments were undertaken at the University Eye Clinic, Mainz (Director, Prof. A. Jess), and others at the Institute of Ophthalmology, University of London (Director of Research, Sir Stewart Duke-Elder), and at the University Eye Clinic, Bonn (Director, Prof. H. K. Müller).

there is proportionately a greater increment in the pressure increase ". Agarwal and Sharma (1953) regarded rises of 7 mm. Hg or more, or a ceiling of over 30 mm. Hg Schiötz, as pathological, and found them in 54 out of 57 eyes with primary glaucoma.

Present Experiments

Methods.—In this paper only drinking tests with 1,000 ml. water are discussed. The patient drank the water in the morning within 5 minutes in a state of fasting. The tension was taken with the Schiötz tonometer 30 minutes and immediately before the test, and 15, 30, 45 and 60 minutes after the patient began to drink. The test was started only if the tension during the preceding 30 minutes had not changed by more than 3 mm. Hg Schiötz. All measurements were done by the author. Treatment with miotics was discontinued 12 hours before the test. Only eyes with primary glaucoma, which had not been operated upon, are used in this paper, besides the normals.

Normal Eyes.—The effect of 318 water-drinking tests was studied in 264 healthy eyes. In this number are included 48 tests which were repeated on another day 15 to 25 min. after the intramuscular injection of 6 Vögtlin-units pituitary hormone (hypophysin). When these results were compared with those obtained in the same eyes without such injections no significant difference was found. Amongst the 318 tests are twelve in which a rise in tension of 6 mm. Hg Schiötz occurred, two with a rise of 7 mm. Hg, one with a rise of 8 mm. Hg, and one with a rise of 10 mm. Hg. A ceiling of 30 mm. Hg Schiötz was reached by five eyes with normal elasticity of the sclera. In all these eyes glaucoma had been excluded by careful examinations.

Glaucomatous Eyes.—The results obtained in eyes with primary glaucoma which had not been operated upon are summarized in the Table.

TABLE

RELIABILITY OF THE WATER-DRINKING TEST IN PRIMARY GLAUCOMA

Initial Tension (mm. Hg Schiötz)	Clinical Form of Glaucoma	No. of Tests	No. of Eyes	Pathological Reactions*			
				Tests		Eyes	
				No.	%	No.	%
30 or Below	Simple	185	106	36	19	28	26
	Chronic congestive	82	53	10	12	10	19
	Acute	19	9	4		4	
	Total	286	168	50	17	42	25
Above 30	Simple	19	16	9	47	9	56
	Chronic congestive	24	21	16	67	14	67
	Altogether	43	37	25	58	23	62

*In this series only rises in tension of 10 mm. Hg Schiötz or more were regarded as pathological. Recent research has shown that " probable pathological results " (rises of 8 or 9 mm. Hg Schiötz) may be differentiated from " definitely pathological results " (rises of 10 mm. Hg Schiötz or more). When both are taken together we find pathological reactions in 32·9 per cent. of the eyes with initial tension below 30 mm. Hg, and 77 per cent. in the group with initial tension above 30 mm. Hg Schiötz.

I. Initial Tension 30 mm. Hg Schiötz or Below.—The Table shows that 286 water-drinking tests were done in 168 eyes. The incidence of positive results was as low as 17 per cent. The percentage of eyes which at one time gave a pathological response after repeated applications of the test was 25 per cent. In another small series of 53 eyes (Leydhecker, 1953), in which as many as 132 drinking tests were done, the incidence of pathological results was 40 per cent. after frequent applications. This seems to be the limit of the reliability of the test if applied to the same patient on different days. These 53 eyes are

included in the numbers given in the Table. As in normal eyes, the injection of pituitary hormone did not influence the results of the test.

II. Initial Tension above 30 *mm. Hg Schiötz.*—43 tests were done on 37 unoperated eyes with primary chronic glaucoma. Although the test was not repeated nearly so often on the same patient as in the previous group and the chance of obtaining a positive result was thus much smaller, the percentage of pathological results was 62 per cent. No selection of cases was made.

III. Influence of Initial Tension.—The importance of the initial tension, which is evident from the comparison between the two preceding paragraphs, is further demonstrated in Figs 1 and 2. Both show water-drinking tests done on the same patient within a fortnight but in Fig. 1 the initial tension was low, while in Fig. 2 it was high in the left eye. A pathological result was obtained only in the second case. No anatomical factors account for the different results in this case, only the physical factor of the initial tension being of importance.

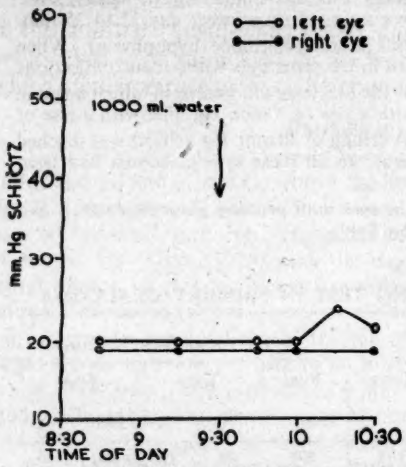

FIG. 1.—Drinking test with 1,000 ml. water. Simple glaucoma.

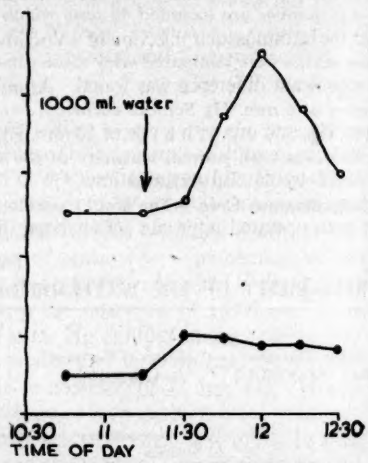

FIG. 2.—Same test with same patient as shown in Fig. 1 on another day.

Fig. 3 shows the results in a patient suffering from bilateral chronic congestive glaucoma of long standing. The chamber angle was wide in both eyes, and in the left there were a few narrow anterior synechiae. The tension in the right eye was normal; in the left it was 35 mm. Hg at the beginning of the test. The water-drinking test was positive in the left eye only. This indicates that the different rise of tension in each eye is not due to the systemic response, as Figs 1 and 2 might lead one to suspect, but that the initial tension is decisive.

The initial tension cannot, however, be the only important factor in the water-drinking test. The tests were negative in glaucomatous eyes when tested in a period of a normal initial tension and again when tension was high. The Table shows that not all eyes with a high tension gave a positive result, whereas there were pathological results in 25–40 per cent. of the eyes with a normal tension.

Discussion

Evaluation of the Test.—The results in healthy subjects agree closely with those of Sugar (1948) who considers a rise of 10 mm. Hg to be pathological and smaller rises are insignificant. A rise of 10 or 12 mm. Hg is no proof of the existence of glaucoma, as is indicated by the results of Honigmund (1951),

Rohrschneider (1952), and by my own case with a rise of 10 mm. Hg, but it is very exceptional amongst normal subjects, and requires a thorough search for glaucomatous symptoms and prolonged observation.

The ceiling is, in my opinion, unimportant when the reliability of the test is discussed. The test works by an increased inflow of water into the eye, which cannot be compensated for speedily enough by an increased outflow in glaucomatous eyes, so that the tension piles up for some time (Leydhecker, 1950). Therefore, if the power of the eye to eliminate fluid through Schlemm's canal is to be tested, only the relative increase of tension is indicative of the degree of obstruction, whereas the ceiling depends also on the initial tension. A rise of 6 mm. Hg from 28 to 34 mm. Hg, for example, is within normal limits and, therefore, not indicative of an obstruction of the outflow. As regards the registration of the test for scientific evaluation purposes, this test would be negative but as regards the diagnosis I would suspect glaucoma, because of the ceiling of 34 mm. Hg and the initial tension of 28 mm. Hg.

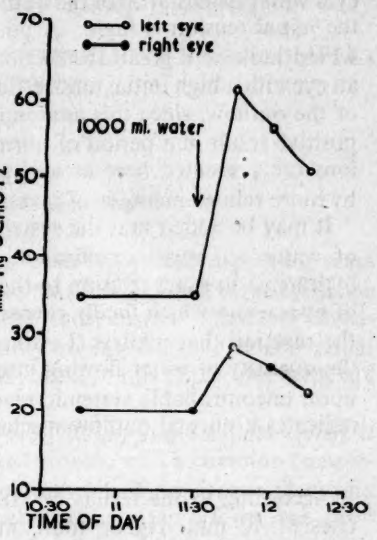

FIG. 3.—Drinking test with 1,000 ml. water. Chronic congestive glaucoma.

Reliability of the Test.—For the reliability of any provocative test the incidence of positive results in unoperated glaucomatous eyes, with an initial tension below 30 mm. Hg is of decisive significance, for this is the field in which we are searching. When we apply the test to a suspected eye, it will always be an eye with a normal tension, since in cases with elevated tension no test is usually required. The very low incidence of pathological results of the water-drinking test in glaucomatous eyes with a normal initial tension has not been pointed out hitherto. The unreliability of this test has been masked by the strong rises of tension which occur in eyes in which it was initially high. How is this influence of the initial tension to be explained?

If we inject the same amount of liquid into an eye with a low tension and into one with a high tension, the increase of pressure will be considerably greater in the latter. The water-drinking test acts in the same way, and the high incidence of pathological results in eyes with an initially high tension is a further proof of the mechanism of the test (Leydhecker, 1950).

Figs 1–3 show that neither a difference in the systemic response on different days nor anatomical factors alone explain the high incidence of positive results in eyes with a supernormal tension. One decisive factor, the height of the initial tension, is mechanical. We have seen that there is a second

important factor, because the initial tension does not explain all the results. This is probably an obstruction of the outflow through Schlemm's canal. In eyes with no hindrance of the outflow, the result is always negative, even when the initial tension is high. A positive result in an eye with normal tension would indicate a great obstruction of the outflow. A pathological result in an eye with a high initial tension does not necessarily indicate a great hindrance of the outflow, since this anatomical factor may not be sufficient to cause a positive result in a period of normal tension (Figs 1 and 2). These conclusions are presented here as a hypothesis, which must be further elucidated by more refined methods of investigation, such as those of Goldmann (1951).

It may be added that the systemic reactions after drinking large quantities of water are very complicated. They by no means consist in a simple hydraemia in exact relation to the ingested quantity of liquid, but the degree of hydraemia which finally causes the increased flow of water into the eye is the reaction that matters (Leydhecker, 1950). It is a serious drawback that the quantity of water flowing into the eye cannot be predicted and depends upon uncontrollable systemic reactions. A negative result, therefore, never indicates a normal outflow mechanism.

Summary

According to the results of 318 water-drinking tests in normal eyes, only rises of 10 mm. Hg or more may be regarded as pathological. In 168 glaucomatous eyes with an initial tension of 30 mm. Hg Schiötz or less, 286 water-drinking tests were carried out, and the incidence of positive results was as low as 17 per cent. Because of the repeated application of the test to some eyes, the percentage of those which reacted pathologically was 25 per cent. In 37 eyes with primary chronic glaucoma and with an initial tension above 30 mm. Hg Schiötz, the incidence of pathological results was 62 per cent., but this is not important, since these eyes require no diagnostic test. In eyes with suspected glaucoma and a normal tension this test is not reliable.

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DEGENERATIONS OF THE DOG RETINA*

IV. RETINOPATHIES ASSOCIATED WITH DOG DISTEMPER-COMPLEX VIRUS INFECTIONS

BY

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BLINDNESS in the dog after distemper has been recognized for many years (Formston, 1952), but unequivocal evidence that it was due to retinal damage has rarely been obtained. It is probable that most cases of blindness associated with such infections are due primarily to involvement of the visual system central to the retina, as in Case 2 reported in this paper, but some are due to degeneration of the retina.

Virus distemper of the dog (Carré, 1905; Dunkin and Laidlaw, 1926) is probably due to a complex of closely related viruses, with a common complement-fixing antigen (Mansi, 1951). Hyperkeratosis of the foot pads occurs commonly but inconstantly in some outbreaks, and this form has been termed " hard pad " disease by MacIntyre, Trevan, and Montgomerie (1948). The term " para-distemper " is used to denote a type of dog distemper in which a high proportion of cases show clinical signs of damage to the nervous system (*Anim. Hlth Trust*, 1949; Parry, 1950). It is possible that inapparent dog hepatitis virus infection may also be involved in some cases of distemper-like illness (Parry and Larin, 1951).

In dogs affected with para-distemper, we have observed chorio-retinal damage of four primary types;

(i) a peracute generalized retinopathy occurring during the initial stages of acute encephalopathy;

(*ii*) a chronic generalized retinopathy in animals showing delayed neurological sequelae, so-called post-infective (distemper) encephalopathy (Parry, 1951);

(*iii*) a dystrophy of the cells of the pigment epithelium with or without evidence of other damage to the retina;

(*iv*) sporadic foci of advanced degeneration of the retina, focal retinal atrophy, and sclerosis.

This paper reports one case of peracute retinopathy after a natural para-distemper infection (Case 1), two cases of chronic generalized retinopathy developing some months after natural para-distemper infection and associated with extensive brain damage (Cases 2 and 3), and observations on dystrophy of the pigment epithelium in twenty dogs affected with natural

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para-distemper infection and in one which went blind after experimental infection (Case 4).

Methods and Material

The methods and terminology employed have been described in previous papers (Parry, 1953a,b,c). Cases 1, 2, and 3 were natural cases diagnosed on clinical and pathological evidence. Case 2 and the twenty cases used for the observations on the pigment epithelial cell dystrophy were natural cases of epidemic para-distemper, which occurred at the Research Station (*Anim. Hlth Trust*, 1949, 1950); in this epidemic the clinical and pathological diagnoses were confirmed by inoculating organ suspensions into ferrets which died or were killed with the lesions typical of this disease from the 12th to 15th day after inoculation (Dunkin and Laidlaw, 1926). Case 4 was a survivor of experimental infection with distemper-complex viruses by Mansi (1951).

The electroretinograms were recorded by the team as described previously (Parry, Tansley, and Thomson, 1953).

Results

(1) Peracute Retinopathy in Severe Para-Distemper

Case 1, a Golden Cocker Spaniel male, 2 years old, weight about 12 kg., was said to have had perfect vision until the onset of a febrile distemper-like illness, when in 3 days it went blind with dilated pupils. When it was examined on the seventh day of illness there was tremor and rigidity of some skeletal muscles, especially of limbs and head, the average pupil size was 12/14 mm., the eye preservation reflex was absent, there were no pupillary light reflexes, the optic media were clear, and there was no day vision. In the fundus the optic papilla and retinal vessels were normal, but there was swirling of the tapetal fundus. Detailed observation of the fundi was difficult owing to an irregular, vertical, oscillatory movement of the eyeball synchronous with a tremor of the upper eyelids. The animal was destroyed with intravenous pentobarbital sodium owing to the severity of the tremors and continued blindness on the 9th day, when hyperkeratosis of the foot pads was marked.

Morbid Anatomy.—The lesions in the parenchymatous organs were similar to those observed previously in para-distemper (*Anim. Hlth Trust*, 1949). The brain and optic nerves were normal macroscopically. The eyes were removed and placed in Kolmer's cold-blooded fluid 10 minutes after death.

Histology.—There was advanced degeneration of the retina and choroid, similar in degree and distribution in both eyes, but at a very much more advanced stage in the retina over the non-tapetal fundus than over the tapetal fundus, where the peripapillary zone (0·5–1 mm. from the papilla) was the least affected. These differences could not be attributed to poor fixation. *Over the peripapillary tapetal zone* the retina was the normal width of about 200 μ and with the normal layers. (Fig. 1).

The pigment epithelium was slightly thicker than normal with an occasional cell of twice the normal thickness. The bacillary layer was thinned, but the precise lesion was difficult to ascertain as the outer limb segments were degenerate and had broken, leaving the layer of stubby inner limb segments only 4–5 μ wide. The external limiting membrane was distinct but in places it had disappeared. The outer nuclear layer was about 50 μ wide and consisted of 8–10 layers of normal rod nuclei, but the larger cone nuclei were not contiguous as is usual and some were pyknotic; furthermore, between the external limiting membrane and the outermost layer of nuclei was a space 7–8 μ wide, in which the radially arranged processes of the rods and cones were plainly visible, producing an eosinophilic zone similar to that seen in the immature retina of the pup and the later stages of *post-mortem* change. The inner nuclear layer was only two to three nuclei thick, with an occasional pyknotic nucleus. The inner and outer fibre layers were essentially normal. The ganglion cells were present but their cytoplasm had undergone marked hyaline change with loss of Nissl substance. The optic nerve fibres were swollen and fragmented, and the internal limiting membrane was thickened.

FIG. 1.—Section of retina of dog with peracute generalized distemper retinopathy (Case 1); peripapillary tapetal fundus. Note that layer organization is normal but that ganglion cells show severe degeneration and outer limbs of rods and cones are reduced in thickness and fragmented (Cf. Fig. 6). Remaining layers essentially normal. Immediate *post-mortem* fixation in Kolmer's cold-blooded fluid. Mallory's phosphotungstic acid haematoxylin. (×180).

The following system of labelling the retinal structures, etc., modified from Polyak (1941), applies to all the Figures:

Sc. Sclera.
Ch. Pigmented choroid.
Tap. Tapetum.
C.C. Chorio-capillaris.
Ret. Retina.
1. Pigment epithelium.
2. Bacillary layer of rods and cones: (*a*) outer limbs, (*b*) inner limbs.
3. External limiting membrane.
4. Outer nuclear layer: (*a*) cone nuclei, (*b*) rod nuclei.
5. Outer fibre layer.
6. Inner nuclear layer.
7. Inner fibre layer.
8. Ganglion cell layer.
9. Optic nerve fibres.
10. Internal limiting membrane.

Over the remainder of the tapetal fundus the retina was much more degenerate, and the outer layers appeared to be folded. Its width was about 100 μ. The degeneration became progressively more severe towards the periphery (Fig. 2).

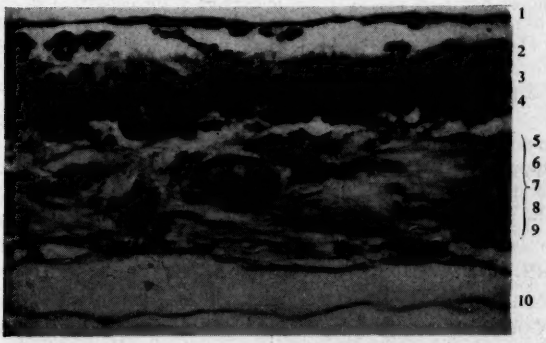

FIG. 2.—Same preparation as Fig. 1; peripheral tapetal fundus. Degeneration much more advanced than in Fig. 1. Ganglion cell and inner nuclear layers have disintegrated leaving thin outer nuclear layer with rods and cones reduced to stubby remnants of inner limbs. (×200).

The rods and cones had disappeared apart from small areas where the remnants of the inner limb segments 3–4 μ wide remained. The outer nuclear layer was four to six nuclei deep. The inner nuclear layer was two to three nuclei thick over the more central mid-tapetal fundus, but gradually

became reduced until it had disappeared at the periphery of the tapetal fundus (Fig. 2). The inner fibre layer was vacuolated. The remaining ganglion cells, which were only present in the central fundus, showed hyalinized cytoplasm, and the optic nerve fibre layer had lost its regular arrangement. The internal limiting membrane was ill-defined. The retinal blood vessels were less numerous but were not obviously abnormal, although buried beneath the surface (Fig. 2).

The central and peripheral non-tapetal fundus showed advanced sclerosis, the retina being 50 μ wide in the mid-ventral fundus and 20 μ in the peripheral fundus (Fig. 3). The remnants of the two nuclear layers were coalesced as a single layer, firmly adherent to the choroid in some places but not in others. No rod and cone layer remained, the ganglion cells had disappeared and the inner fibre and nerve fibre layers remained as a combined fibre layer with a few glial nuclei. Large round cells, containing dark brown round granules of pigment and distributed irregularly throughout the remnants of the retina, were numerous in some fields (Fig. 3).

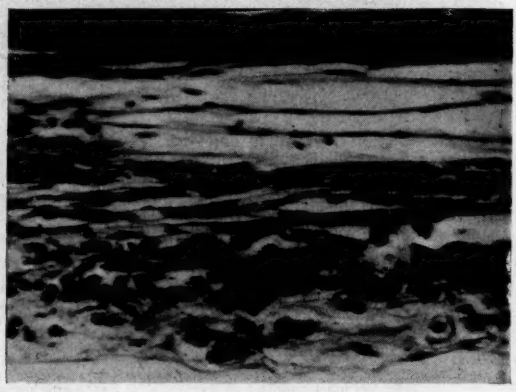

FIG. 3.—Same preparation as Figs 1 and 2; peripheral non-tapetal fundus. Retina completely sclerosed, with no sign of layer organization. Note large round cells filled with dark-brown pigment in sclerosed retina. No pigment epithelium remains. Choroid has lost much pigment and is much thinned. (×200).

The choroid over the whole fundus was reduced in width to about 100 μ wide, and its cells contained much less pigment than usual (Fig. 3); some of the larger arteries showed vacuolation and degeneration of the media, and the endothelial cells lining some of the venous sinuses were swollen.

The *optic papilla* was raised gradually towards the centre through swelling and fragmentation of the nerve fibres, but there was no abrupt thickening at the papillary margin. The optic nerve head showed increased numbers of glial cells and the nerve fibres had lost their regular arrangement and in places were markedly vacuolated; there was considerable perivascular exudate around the central vessels.

Comment.—There is a severe generalized chorio-retinal degeneration which has developed presumably within 9 days. In the retina the severity of the degeneration is not symmetrical, the non-tapetal fundus being more severely damaged than the tapetal. The degeneration appears to have developed from the periphery to the centre of the fundus, and, within the retina, from the optic nerve fibre layer outwards and from the rods and cones inwards at the same time, leaving the two nuclear layers to be affected last.

(2) CHRONIC DELAYED RETINOPATHY AFTER PARA-DISTEMPER.—Although we have seen a number of cases, which may be placed in this category on clinical grounds alone, we have two cases only which have been under adequate supervision and have come to autopsy, thereby allowing a pathological confirmation of the clinical diagnosis.

Case 2 (DO 18), a Red Irish Setter bitch, sent to the Research Station for observation when 4 months old was an unaffected offspring of a test-mating for suspected hereditary retinal degeneration (Hodgman and others, 1949). When a year old she was severely ill

during an epidemic of para-distemper (*Anim. Hlth Trust Rep.*, 1949) with signs of acute disseminated encephalopathy, which persisted for 7–10 days, after which she made a complete recovery without immediate residual neurological defects. Day and night vision and the fundus were normal until she was about 2 years old, when her vision was noticed to be defective by day and night. However, the average pupil size was not greatly increased, although the pupillary light reactions were sluggish. The fundus was normal although the texture was not as beaded as usual. When 26 months old the electroretinogram was recorded using contact electrodes, a small potential was recorded from the left eye but none from the right eye.

About this time she became very timid and refused to play with her companions, wandering about aimlessly. During the following 6 months her mental condition and sight gradually deteriorated until, when 2½ years old, she was almost totally day and night blind. The average pupil size of both eyes was still 6/14 mm., the pupillary light reactions were still present, the lenses and media were clear, but the fundi were abnormal. There was loss of retinal blood vessels: the smaller vessels were not seen, while the outlines of the larger vessels were indistinct as if they had become partly buried. The tapetal fundus was slightly crystalline but the stellulae of Winslow were unusually prominent. The optic papillae were white, but both the primary and secondary blood vessels were still present. The clinical diagnosis was that the fundus changes did not account for the severity of the visual defect, and that damage to the central nervous system was also present, to which the mental deterioration could also be attributed.

The dog was destroyed by intra-vital injection of Kolmer's cold-blooded fluid under pentobarbital sodium anaesthesia.

Morbid Anatomy.—Damage to the brain was confirmed at autopsy when widespread cavity formation in the cerebral cortex, especially of the occipital poles, was found, together with advanced demyelination of the optic nerves and chiasma. The eyes were normal when opened.

Histology.—There was *a generalized chorio-retinal degeneration* in both eyes, which was remarkably regular in severity apart from small foci of more advanced damage to the retina. The principal retinal lesions were in the first-order neurones and the nerve fibre layer with hypertrophic dystrophy of the tapetal pigment epithelium.

Over the whole fundus except the extreme periphery the retina was only about 120 μ wide. The outer nuclear layer was reduced to 12–15 μ wide and three to five nuclei thick, through loss of rod nuclei, some of which could be seen fragmenting along the inner margin. The majority of the cone nuclei were normal.

The rod and cone layer was also reduced to about one-third of normal, being 10 μ wide, the outer and inner limb segments being about 5 μ each, although in places the inner limbs were shorter than the outer. The individual outer limbs were of uneven thickness and in many places were fragmented. The cone inner limbs were foreshortened and stubby, while the number of rod inner limbs was reduced to about half. There were also foci 150–200 μ wide where the outer limbs had almost disappeared. The outer fibre layer was much reduced in width, being about 7–8 μ wide. The inner nuclear layer was essentially normal, being 15–18 μ wide and four to five nuclei thick, but the nuclei of Müller's fibres were more conspicious than normal and stained more deeply with most stains.

The ganglion cells were still present, although their number was reduced, particularly in some areas, but the cytoplasm of the surviving cells was disintegrating with loss of Nissl substance, and in many the nuclear membrane had disappeared. The nerve fibre layer was much widened, being 30–35 μ thick even over the mid-tapetal zone; the thickening persisted as far as the periphery. Müller's fibres were greatly thickened (gliosis) and the bundles of the intervening nerve fibres were swollen and disintegrating. The smaller retinal blood vessels were buried in the thickened nerve fibre layer, and their walls were thickened and ill-defined. The internal limiting membrane was very conspicuous, being about 2·5 μ thick.

The tapetal pigment epithelial cells were about twice their normal size, with deep brown granular cytoplasm which stained blue with the azan method; about 500 μ apart in a section were one or two giant pigment epithelial cells 10–15 μ in diameter, adjacent to which the rods and cones were greatly reduced. The normal lanceolate pigment granules of the non-tapetal fundus were present. Occasionally there were multi-cellular " nests " of pigment cells, adjacent to which the

rods and cones were lost; the pigment cells were free of pigment and the centre and base of the "nest" showed hyaline changes (Fig. 4). The tapetum was normal in the left eye but in the right eye the cells were swollen and oval, and reduced in number, and the trans-tapetal capillaries were 2-3 times their normal width.

FIG. 4.—Section of retina of dog with chronic delayed generalized post-distemper retinopathy (Case 2); dorsi-ventral non-tapetal fundus. Note multicellular "nest" in pigment epithelium composed of enlarged pigment epithelial cells free of pigment. Outer central portion comprises an eosinophilic hyaline mass. Note complete atrophy of adjacent rods and cones. Intra-vital fixation with Kolmer's cold-blooded fluid. Mallory's phosphotungstic acid haematoxylin. (×250).

In addition to the generalized degeneration described above, there were foci of *more advanced change*. In the left eye, there was a focus 150 μ long over the mid-tapetal fundus where the retina was only 100 μ wide, the rods and cones had disappeared, and the outer nuclear layer consisted of a single layer of cone nuclei (Fig. 5).

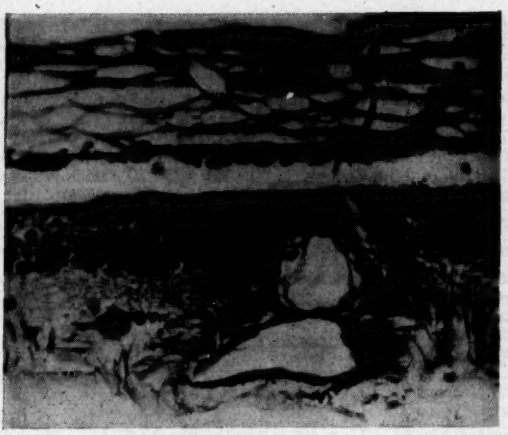

FIG. 5.—Same preparation as Fig. 4; mid-tapetal fundus. Small focus adjacent to a large retinal artery and vein of more advanced atrophy in which rods and cones have disappeared and cone nuclei only remain in outer nuclear layer. Few inner limbs of cones present on right. (×250).

The extreme ventral periphery inwards for about 200 μ from the ora serrata showed advanced sclerosis with infiltration of round pigment cells similar to those seen in Case 1 (Fig. 3). The *choroid* all over the fundus was thinned slightly to 100 μ and its blood sinuses were greatly reduced. The optic papilla was contracted outwards and the optic nerve showed severe degeneration of nerve fibres with advanced demyelination.

Comment.—The generalized chorio-retinal degeneration was less advanced in this case than in Case 1. The outer nuclear and rod and cone layers were affected most severely, but the optic nerve fibre layer was also gliosed and degenerate, probably due to centrifugal degeneration from the optic nerves in which demyelination was severe and to which the early degeneration of the ganglion cells may possibly be due. There was a simple hypertrophy of the tapetal pigment epithelium with abnormal pigmentation and occasional multicellular " nests " occurred in which pigment changes were absent.

Case 3 (DH O1), Cocker Spaniel male, a house pet, weighing about 12 kg., had a history of a mild febrile illness coinciding with an epidemic of distemper in the district about 6 months before defective day and night vision was noted at 18 months old. When examined at 2 years old both eyes were similar. The dog was partly day blind, and almost completely night blind: the average pupil size was 8–9/14 mm., and the pupillary light and corneal reflexes were normal, but the eye preservation reflex was absent. The lens and media were clear. The retinal blood vessels were inconspicuous and the papillae were white, especially the left where only the horizontal branches remained. In the extreme ventral portion of the non-tapetal fundus of the left eye were two small white plaques, 1–2 mm. in diameter and with discrete but irregular margins, thought to be due to defects, probably exudate, in the choroid. Examination of the nervous system revealed no other defects apart from a slight ataxia associated with asthenia of the limbs without disturbances of reflexes.

The choroid defects disappeared over the ensuing 3 months, but vision became worse. At 2½ years the dog was apparently completely day and night blind (average pupil size 12/14 mm., pupillary light reflexes absent) and the tapetum showed an enhanced green reflection and a crystalline texture. The ataxia was now more marked, and there was some loss of reflexes. Over the next year some mental and emotional deterioration occurred and the ataxia due to atonia and dysmetria of the hind limbs became worse. The dog was kept under observation until it was 3½ years old, *i.e.* 2 years after the visual defect was first noted, when it was destroyed by intravenous pentobarbital sodium without intra-vital fixation.

Morbid Anatomy.—At autopsy slight general atrophy of the cerebral hemispheres was found, but the optic nerves were normal. The eyes were placed in fixative within 15 minutes of death and were normal when opened.

Histology.—There was advanced sclerosis of the retina over the whole fundus in both eyes similar to the peripheral portions of Case 1 (Fig. 3), but in addition the pigment epithelium was thickened regularly to about 10 μ wide over the whole fundus except the extreme periphery; the cytoplasm of the tapetal pigment epithelial cells was filled with a yellowish-brown granular pigment, while that of the non-tapetal cells was more heavily charged with lanceolate granules than normal. Occasionally a round pigment cell was seen in the sclerotic retina. The tapetum was thin and the choroid was reduced in width to less than 100 μ over much of the fundus. The optic nerves showed advanced degeneration with demyelination.

Comment.—Although direct biological evidence was not available to confirm the clinico-pathological diagnosis of para-distemper in this case, the similarity of the retinal lesions to those of Cases 1 and 2, the dystrophy of the pigment epithelium, and the associated brain lesions strongly suggest that they may all be attributed to a previous distemper-complex virus infection.

(3) HYPERTROPHY OF PIGMENT EPITHELIUM AFTER NATURAL PARA-DISTEMPER.—We have examined the eyes of nineteen dogs which died or had to be destroyed owing to peracute and acute para-distemper 2 days to 2 months after the clinical illness began. Of these, seventeen were affected in the natural para-distemper epidemic at the Research Station, and two were dogs sent to us while incubating the disease.

Fifteen were Red Irish Setters, of which seven were affected with Stage 2 hereditary progressive retinal degeneration (Parry, 1953 b), three were Greyhounds, and one was a Poodle. Their ages ranged from 3 months to 3 years. In none was any specific visual defect attributable to the virus infection noted during life, although some of those dying of the peracute disease showed signs of coma and diffuse encephalopathy. The majority of eyes were obtained at autopsy after natural death and were therefore unsuitable for studying fine changes in the retina.

Histology.—Changes in the pigment epithelium were observed in eight of the twelve dogs with normal retinae; no changes were observed in the seven dogs affected with the hereditary degeneration, in which the pigment epithelium was very largely missing, or in two Greyhounds, one Setter, and the Poodle, all of which died within 2–4 days of the onset of the disease. The seven normal Setters and one Greyhound, in which the changes in the pigment epithelium occurred, all survived more than 4 days of clinical illness, those with the most marked lesions surviving the longest. The changes occurred symmetrically in both eyes. The earliest stage was a swelling of the pigment epithelial cells over the tapetal fundus to a width of 7–8 μ and the development of a brownish granular cytoplasm staining a deep blue with the azan method. At first only a few individual cells were affected, but in later cases the whole pigment epithelial layer over the tapetal fundus (Fig. 6)

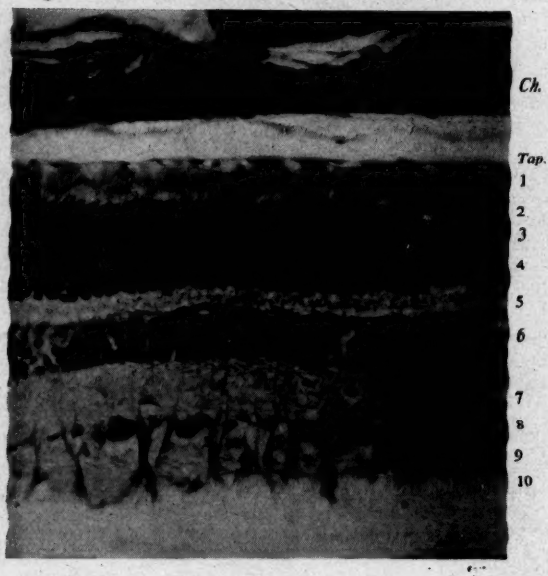

FIG. 6.—Section of retina of dog with dystrophy of pigment epithelium after para-distemper (Case 3); peri-papillary tapetal fundus. Note hypertrophy of pigment epithelial cells, causing early compression atrophy of adjacent rods and cones. Remainder of retina normal. Intra-vital fixation with Susa's fluid. Mallory's phosphotungstic acid haematoxylin. (×250).

was 15–20 μ wide with cytoplasm heavily charged with the light-brown granular pigment, while that over the non-tapetal fundus was thickened to 10 μ, but without the granular pigmented cytoplasm; the usual lanceolate pigment granules were still present. In five cases which had survived 2 to 3 weeks and had been destroyed on account of other disabling neurological sequelae, the tapetal pigment epithelium was 20–25 μ wide all over the fundus, and the rod and cone outer limbs were reduced in length to 6–7 μ, but the other parts of the retina appeared to be normal.

Comment.—Dystrophy of the pigment epithelium, particularly of the tapetal fundus, can be a sequel to clinical para-distemper if the dog survives 3 to 4 days of clinical illness; the pigment epithelial cells show hypertrophy and unusual pigmentation. The hypertrophy causes secondary pressure atrophy of the outer limbs of the rods and cones.

(4) Hypertrophy of Pigment Epithelium after Experimental Inoculations with Dog Distemper-Complex Virus.

Case 4, a white Alsatian male, was infected intra-nasally and subcutaneously at 3 months (by Dr. Mansi) with a strain of Laidlaw-Dunkin distemper maintained for five intracerebral-ferret passages. From the 4th to the 9th day thereafter the dog had a febrile illness with diarrhoea. On the 8th day it was noticed to be blind, but vision had apparently been recovered completely by the 18th day, when its general health was normal. Between the ages of 5 to 8 months the dog was inoculated four times with the " Glasgow S. 123 " strain of dog-distemper virus without any signs of ill-health except that gradual impairment of vision was noticed again towards the end of this period. It was examined when 9 months old. The general health of the animal was excellent. The average pupil size was 5/14 mm., the pupillary light reactions were brisk, the eye preservation reflex was absent, and day vision tests indicated that the dog was totally blind. The eyeballs, lens, media, and fundi were normal. Clinical observation suggested that the blindness was due to damage central to the lateral geniculate body.

The dog was destroyed by intravital injection with Kolmer's cold-blooded fluid under pentobarbital sodium anaesthesia.

Morbid Anatomy.—The parenchymatous organs were normal, although liver adhesions were suggestive of a previous canine hepatitis virus infection (Parry and Larin, 1951). The optic nerves and spinal cord, brain stem, and cerebellum were normal, but there was widespread cavitation in the right temporal and pyriform lobes, *i.e.* in those parts supplied by the middle cerebral artery.

Histology.—There was a modest retinal degeneration. The retina was about 150 μ wide; its general organization and cytology were normal apart from minor changes in the pigment epithelium, optic nerve fibre layer, and some ganglion cells.

The tapetal pigment epithelium was slightly hypertrophied, being 7–8 μ wide, while some individual cells in all parts of the fundus were more enlarged, being 20 μ long and 15 μ wide. In the tapetal fundus these enlarged cells were much more frequent and in places had caused atrophy of the adjacent outer limbs of the rods and cones; they had a brownish granular cytoplasm which stained a deep blue by the azan method. The normal lanceolate pigment granules over the non-tapetal fundus were prominent and were continued centrally beyond the junctional zone, where the pigment epithelium is usually unpigmented. No multi-cellular " nests " were seen.

The nerve fibre layer for 1 to 2 mm. adjacent to the papilla was fragmented and shrunken, and over this area the ganglion cells were reduced in number, and many surviving cells were degenerating; their nucleus and cytoplasm had lost their sharp demarcation and the small Nissl's granules had coalesced into eight to ten larger granules in each cell. More peripherally the ganglion cells appeared normal, but there was slight swelling of the nerve fibre layer with vacuolation and waviness indicative of early degeneration. The optic nerve showed marked fragmentation and waviness of the nerve fibres. The choroid was about 120 μ wide and its blood vessels were normal.

Comment.—This case shows modest choroidal atrophy, dystrophy of the retinal pigment epithelium, peripapillary degeneration of the nerve fibre layer, and loss of ganglion cells near the papilla with early optic atrophy. The absence of marked retinal changes confirm the opinion based on the clinical signs that the blindness was of non-retinal origin. The

hypertrophy and the pigment dystrophy of the pigment epithelial cells were very similar to those seen in natural cases of distemper-complex infection.

Discussion

The literature on the role of virus infections in degenerations of the retina is scanty (Perdrau, 1940; Sorsby, 1948). In man there is the great difficulty of obtaining pathological confirmation of clinical observations, while in animals, although the association between dog distemper and blindness has for long been recognized, few attempts to determine the locus of the responsible lesion have been published. The observations reported in this paper provide evidence that the dog distemper virus can cause serious damage to the dog retina either during the acute phases of the disease, or as a delayed sequel to the infection. These observations seem of particular interest in view of the recent clinical reports of acute retinopathy in man following non-fatal infections with the virus of Rift Valley fever (Schrire, 1951; Freed, 1951).

The distribution and sequence in which the damage occurred in these cases of distemper retinopathy suggests that the chorio-retinal damage may be of two types: related to direct damage to the tissues or their blood supply, or related to pre-existing damage to the optic nerves.

(*i*) The retina may be affected from both the choroidal and vitreal surfaces simultaneously, causing atrophy of the first- and third-order neurones before the second-order neurones;

(*ii*) Degeneration of the optic nerves cranial to the papilla is followed by retrograde degeneration of their retinal connections, which causes a degeneration, proceeding centrifugally from the papilla, of the optic nerve fibre layer and later of the ganglion cells. A somewhat similar pattern of degeneration is seen in glaucomatous retinopathy, but damage to the third-order neurones proceeds simultaneously all over the fundus in the dog, and is probably most marked at the periphery. This second type of distemper retinopathy is probably analogous to that seen after the severing of the optic nerve in man (Landolt, 1872; Litten, 1882), although no data relating directly to dogs have been found.

Peracute Retinopathy after severe para-distemper infection (Case 1) showed generalized damage to the retina, of the first type, which was least marked over the tapetal peripapillary zone and most marked over the peripheral non-tapetal fundus. The damage presumably occurred within 9 days. All layers of the retina were apparently affected together, since the loss of rods and cones was contemporaneous with the loss of bipolar nuclei and changes in the ganglion cells and their nerve fibres. The separation of the rod and cone nuclei from the external limiting membrane is unusual, and it is not clear whether this was due to loss of cone nuclei or whether retraction of the retina inwards drew the inner limbs of the rods and cones partly through the membrane. Certainly the remnants of the cones appear swollen at their outer ends, as if cone substance had been partly drawn inwards, an effect we have

not observed in any other sections prepared in a similar manner. The more advanced stages over the non-tapetal fundus show the varying degrees of sclerosis observed in the other types of retinal degeneration in the dog.

The atrophy of the choroid and the changes in the walls of its blood vessels suggest that an important factor in peracute para-distemper retinopathy is interference with the choroidal blood supply. The damage to and burying of the retinal blood vessels and the oedema around the central vessels of the optic nerve suggest that the damage arising from the inner surface of the retina may also be related to disturbances of blood supply. It is interesting that no intracellular inclusion bodies were seen which would indicate direct parasitization of retinal cells by a virus.

Chronic Delayed Retinopathy (Cases 2 and 3), following the virus infection after a considerable latent period and with a co-existing degenerative encephalopathy, illustrates both primary and secondary types of retinopathy which can conveniently be termed " post-infective " (Parry, 1951). The precise relationship of the virus infection to these degenerations is not known, since virus cannot be detected after the acute phase of the illness in this type of case. These cases, in which both retinal degeneration and epithelial cell dystrophy occurred, are of particular interest when considered in conjunction with the cases of simple pigment epithelial cell hypertrophy and that of delayed retinopathy after experimental inoculations of virus (Case 4). It seems probable that they may represent different stages of a single disease process. In Case 2 the rods and cones were probably still partly functional, the visual defect being due mainly to damage in the optic pathways, a view supported by the recording of an electro-retinogram from one eye after day-blindness was advanced. The degeneration appears to affect the rod nuclei near the inner edge of the outer nuclear layer and takes the form of a fragmentation of the chromatin, followed by lysis, but without infiltration of inflammatory cells. At the same time, both outer and inner bacillary layers were reduced in width, and the ganglion cells and optic nerve fibres of the central retina disappeared, leaving the second-order neurones relatively intact. Coinciding with the loss of all the rod nuclei, the two nuclear layers coalesced, the ganglion cells gradually disintegrated, and the normal layer organization of the retina was lost, as in the advanced stages of other retinal degenerations. In Case 3 the degeneration was so advanced that it was not possible to determine the sequence of its development, but it is noteworthy that the dystrophy of the pigment epithelium remained similar to that seen in the earliest cases, *i.e.* once it has developed it persists probably indefinitely.

Focal Degenerations (Case 2) were of two types :

(*i*) foci of more advanced atrophy of rods and cones and their nuclei over areas 0.5–1 mm. wide;

(*ii*) focal sclerosis involving disorganization of all layers of the retina and similar to the advanced sclerosis of the ventral non-tapetal fundus.

We have seen similar sclerotic foci in a case of central retinal degeneration with a history of para-distemper in puppyhood, small foci of both types in an otherwise normal horse retina, and foci of atrophy only in a tiger's retina. The foci of atrophy appear to be very similar to those seen in the rabbit by Tansley (1951), and in the rat, mouse and ferret (Tansley, 1952) in the aetiology of which there is no reason to suspect a virus infection, and to the so-called "focal" pseudo-retinitis pigmentosa observed in a boy of 18 by Cogan (1950, Fig. 36). An acute focal retinitis with inflammatory cell infiltration was observed by Overman and Dortch (1951) after the intra-ocular inoculation of rabbits with Semliki Forest virus, which they attributed to the direct action of the virus on the retina; it is possible that these acute inflammatory foci might have developed into foci of sclerosis if their rabbits had been allowed to live long enough. However, we have seen no abnormal mitoses in the outer nuclear layer such as they described, possibly because our cases were not examined early enough. In all the dog cases there has been a history of distemper-complex infections, and although the aetiology of these focal lesions is not established, their occurrence in these dogs does suggest that they may be related to some enhanced local action of the virus infection. It seems likely that the rod-free foci described by Zürn (1902) as a fovea in the dog may have been foci of degeneration.

The advanced sclerosis seen in Cases 1, 2, and 3, in which the retinae lie adjacent to the choroid without intervening pigment epithelium, are virtually identical with that seen in the advanced stages of hereditary atrophy (Parry, 1953b). The use by Cogan (1950) of adhesion and non-adhesion of retina and choroid as a distinguishing feature between hereditary and inflammatory lesions seems hardly warranted, and bears out the contention of Tansley (1951) that it is an unreliable criterion.

The case of blindness following experimental distemper-complex infection (Case 4) is primarily one of blindness due to damage in the brain central to the lateral geniculate body, but the changes in the retina with very early centrifugal degeneration of the peripapillary ganglion cells and the dystrophic pigment epithelial cells causing slight compression of the adjacent outer limbs are very similar to the lesions seen in the cases of natural para-distemper infection. It seems not unlikely that the retinal changes in this case illustrate an early stage of a disease process of which Case 2 is an example of a later stage, possibly related to the longer interval of 18 months since the primary virus infection in Case 2 compared with 6 months in Case 4. It is interesting to speculate on the role of the repeated exposures of Case 4 to virus in the development of the degenerative process.

Dystrophy of the Pigment Epithelium, seen in many dogs without serious damage to the retina, consisted of a simple hypertrophy with abnormal pigment formation, and was most prominent in the usually pigment-free tapetal pigment epithelium.

The hypertrophy took two forms :

(*i*) *modest generalized regular hypertrophy* (Fig. 6);
(*ii*) *massive irregular focal hypertrophy*, affecting foci of from one to about twenty contiguous cells.

In the first type of hypertrophy the radial width of the tapetal cells was 8–10 μ (a two to three fold increase), and their retinal and choroidal surfaces were approximately parallel. In the second type, the individual cells were 20–25 μ long and 15–20 μ wide, and their retinal surface was convex and pressed severely on the adjacent outer limbs.

The pigment abnormalities were also of two types:

(*i*) the occurrence throughout the cell body of round refractile golden-brown pigment granules which stained a deep blue with azo-carmine,
(*ii*) an increased quantity of the dense dark-brown lanceolate pigment granules normally present over the non-tapetal fundus.

Pigment cell dystrophy of these types is not a feature of the normal dog retina, nor does it follow *post-mortem* change (Parry, 1953a); indeed, the eyes of several of the cases examined were fixed intra-vitally or within 5 minutes of death. It is difficult not to attribute them to the effect of the virus infection on the pigment epithelium, since they can occur without retinal damage. The atrophic epithelium seen in the later stages of the hereditary retinal atrophy is not affected. Whether the dystrophy is a common reaction we do not know, but it may be significant that the strains of distemper-complex virus involved all produced damage to the nervous system. It is also of interest, if we accept the evidence of Cases 2 and 3, that once the dystrophy is initiated it apparently persists without much change for at least 2 years. If this deduction is confirmed, the presence of this dystrophy might prove of value as an indication of previous distemper-complex infection.

The effects of the dystrophic pigment epithelium on the maintenance of the integrity of the retina are not well understood. In areas where the epithelium was 25μ wide, the outer limbs of the rods and cones were undergoing simple pressure atrophy, while the remainder of the retina appeared to be normal. However, the dystrophic epithelium may well interfere with the normal extravascular circulation to the rods and cones from the chorio-capillaris in areas where no such atrophy is apparent. Pigment epithelial cell dystrophy also occurs in the syndrome of central retinal degeneration (Parry, 1953d), in which in addition to the general hypertrophy, large multicellular " nests " of pigment cells occur. These " nests " can be detected on ophthalmoscopic examination of the fundus, while the hypertrophy associated with distemper-complex infections cannot; multicellular " nests " do not occur regularly in the simple para-distemper syndromes, although an occasional one without pigment but showing hyaline degeneration occurred in the case of chronic retinopathy (Case 2, Fig. 6).

These dystrophic pigmented cells, obviously derived from the pigment

epithelium, should be distinguished from the pigmented cells of less obvious origin which invade the remnants of the degenerating retina when sclerosis is far advanced as in Cases 1, 2, and 3 (Fig. 3). The latter occur in retinal sclerosis of varying aetiology, *e.g.* that following the hereditary atrophy; they are usually about 30 μ in diameter, round, and loaded with dark-brown, round pigment granules which like those of the choroidal cells remain unstained by the azan method. They are hence quite different in size, shape, and pigment characteristics from the pigment epithelial cells, and no intermediate types have been seen. The pigment cells in sclerosed retinae correspond closely with the rounded cells with round, dark-brown chromatophores which occur in the degenerating choroid, and it seems most likely that these modified pigmented cells from the choroid migrate into the sclerotic retina in the advanced stage of many chorio-retinal degenerations.

The fact that pigmentary aberrations with retinal degeneration may follow distemper-virus infection in the dog (which is usually associated with fever and affections of the respiratory tract, and less commonly with damage to the nervous system) makes one ponder whether some human cases of slow loss of vision with pigmentary changes of the retinitis pigmentosa type may not be related to previous virus infection, say of influenza B, in some epidemics of which cases showing nervous signs may occur (Leigh, 1946)

Summary

(1) Chorio-retinal degenerations following natural and experimental infection with viruses of the dog distemper-complex in the dog are described. Four main types of primary distemper retinopathy are recognized:

(*i*) The infection may cause a peracute generalized primary degeneration (retinopathy) with bilateral day and night blindness of sudden onset.

(*ii*) A chronic generalized primary retinopathy with gradual loss of day and night vision may develop slowly 1 to 2 years after the primary infection.

(*iii*) A dystrophy of the pigment epithelium characterized by hypertrophy and aberrant pigmentation without other retinal damage may occur; this is most prominent over the tapetal fundus.

(*iv*) Small foci of degeneration, either of atrophy or of sclerosis, are also encountered; their possible origin is discussed.

(2) A subsidiary type of retinopathy secondary to atrophy of the optic nerve is characterized by a centrifugal degeneration of the optic nerve fibre layer and of the ganglion cells.

(3) In both types of generalized primary retinopathy (1, *i* and *ii*) the peripheral fundus is affected more severely than the central fundus, and the degeneration appears to proceed into the retina from the inner and outer surfaces simultaneously. The possible relationship of this distribution and sequence to the blood supply is considered.

(4) The origin of the pigmented cells found in the sclerosed retina is discussed.

It is a pleasure to acknowledge once again the collaboration of Dr. Katherine Tansley and Dr. L. C. Thomson with the electroretinography. I am also indebted to Dr. Tansley for advice on the histology and to Mr. C. F. Hart for his skill in the preparation of the sections.

I am especially indebted to Dr. Mansi and Mr. J. R. Hudson of the Ministry of Agriculture's Veterinary Laboratory at Weybridge for their kindness in drawing my attention to Case 4, and in allowing me to quote details from their experimental protocols.

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INTRANASAL RHINO-DACRYO-CYSTOSTOMY FOR PERSISTENT EPIPHORA IN CHILDHOOD*

BY

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London

THE problem of the persistently watering eye in childhood presents different aspects from the similar condition in later life. The watering seems to worry the child most of the time and not to be confined to stimulus by cold air as is often the case in adults. Infection is prone to occur and is difficult to control. The small size of the lacrimal apparatus makes probing difficult, and necessitates general anaesthesia on each occasion.

No attempt will be made in this annotation to discuss the aetiology or pathology of this condition: the intention is simply to describe a procedure which has been found useful.

Probing and dilatation by the ophthalmologist will result in a cure in the majority of cases, but occasionally repeated probing and dilatation fail to result in a satisfactory outcome. It is in these cases that a further procedure is necessary.

It appeared to me that the usual operation of the external approach to the lacrimal apparatus, such as is used in later life, was less acceptable in young children, since a scar on the developing face, however inconspicuous, is to be avoided if possible. Consequently I decided to employ the intranasal approach.

There is nothing original in the concept of the intranasal approach to the lacrimal sac; it has been described for many years, but there are some modifications of technique which I have used for these children. The operation is not difficult in spite of the smallness of the nose in childhood.

Operative Technique

Half an hour before operation the affected side of the child's nose is packed with ribbon gauze which has been wrung out in a solution of 10 per cent. cocaine and 1:1,000 adrenaline, equal parts. General anaesthesia is used, with an intra-tracheal tube, around which is a pack to prevent any secretion entering the bronchial tree.

An expanding Killian speculum is inserted into the nostril on the affected side, and opened as wide as possible, and the pack, which was placed *in situ* before the anaesthetic, removed. 2 minims 1:1,000 adrenaline in 0·5 ml. normal saline is then injected under the muco-periosteum in the area immediately anterior to the middle turbinal. A quadrilateral piece of muco-periosteum is then cut out and removed completely in the area shown in the diagram, using a small knife. There is no possibility of performing any intranasal suturing of the nasal muco-periosteum to the lacrimal sac in the small area of a child's nose, but it is very important that

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the muco-periosteal square be completely removed, leaving bare bone underneath. This bone is now removed, using at first a curved gouge for the initial cut, and after that, punch forceps, so that all bone corresponding to the muco-periosteal square, is removed.

A probe is then passed through the canaliculus of the lower lid and into the lacrimal sac, which is dislocated as far as possible into the nose through the newly-fashioned hole. As much as possible of the internal wall of the lacrimal sac is then cut away, using small curved scissors, so that a wide channel is formed, bounded on the outer aspect by the lateral wall of the sac, and leading into the nose through the opening already made in front of the anterior end of the middle turbinal. A pack of ribbon gauze is then placed in the nostril, and this is removed after 12 hours.

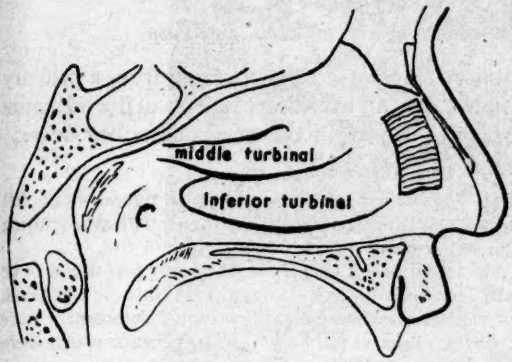

FIGURE.—The portion of muco-periosteum and underlying bone to be removed is shown by the shaded area.

Syringing from the canaliculus to the nose is performed on the day following operation, and repeated daily for a week. No further treatment is needed.

Recently a follow up was conducted on seven cases which had undergone intranasal rhino-dacryo-cystostomy during the years 1949–1951. All the cases had dry eyes, and none of the ostia had closed. The patients' ages varied from 3 to 8 years, and all had had repeated probing and dilatation under general anaesthesia before the rhino-dacryo-cystostomy.

I am grateful to my colleague, Mr. J. H. Doggart, for referring these cases to me.

Brit. J. Ophthal. (1954) 38, 312.

CASE NOTES

CHOROIDAL CARCINOMA METASTATIC FROM THE MALE BREAST*

BY

C. H. GREER

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GIRI (1939), reporting a secondary carcinoma in the choroid from a primary growth in the male breast, stated that an exhaustive search of the literature had revealed no previous instance. An additional case is described below.

Case Report

Male ultramarine worker, aged 41.—In October, 1943, biopsy from a tumour in the left breast showed a spheroidal-celled carcinoma, and a radical mastectomy with skin grafting was performed followed by deep x-ray therapy.

In March, 1951, episcleritis developed in the left eye; the visual acuity was found to be 6/6 and the episcleritis settled under local treatment. By August, 1951, this eye was blind, but not painful, and examination showed an extensive shallow retinal detachment from 4 to 10 o'clock with ballooning of the retina at about 6 o'clock, beneath which there appeared to be a solid mass near the ora serrata. The eye was enucleated on the suspicion of primary choroidal neoplasm. Further examination of the patient, however, revealed several shadows in the left lung, left phrenic paralysis, and extensive osteoclastic changes

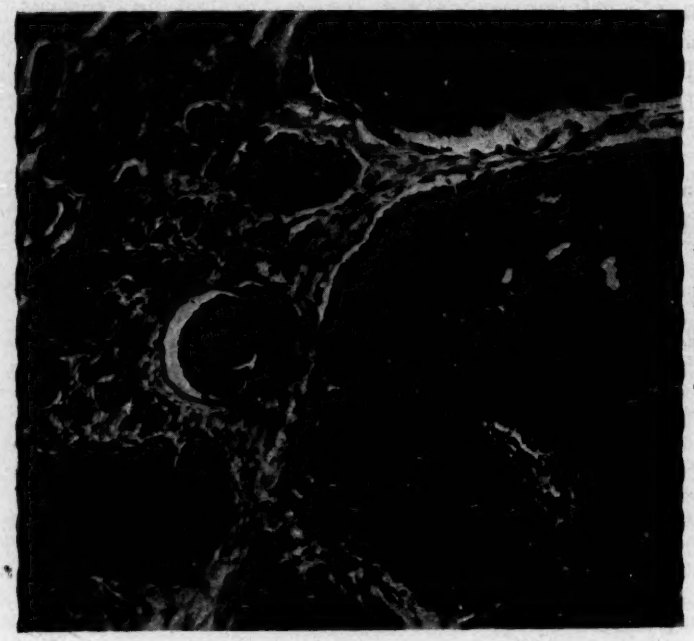

FIG. 1.—Metastatic spheroidal cell carcinoma in the kidney, from a primary in the male breast. Haematoxylin and eosin × 120.

*Received for publication August 7, 1953.

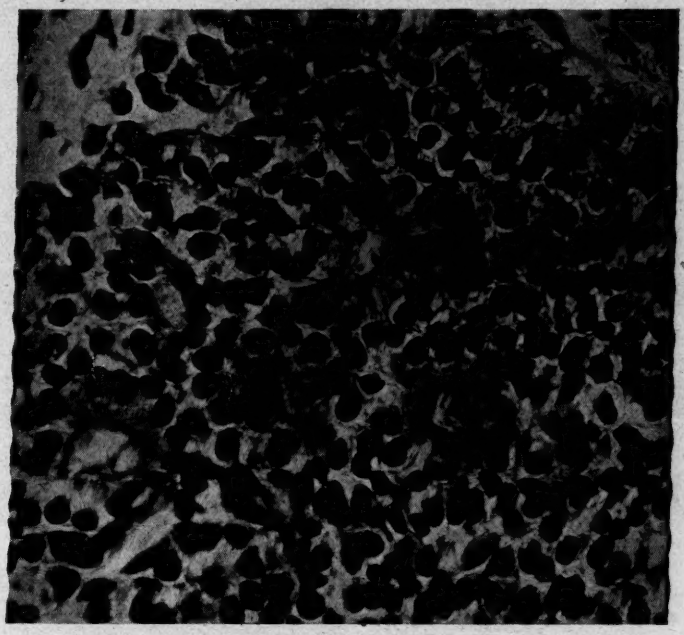

FIG. 2.—Detail from Fig. 1. ×500.

in both femora. In December, 1951, he was admitted to hospital with a pathological fracture of one femur, and he died in May, 1952.

Post-Mortem Findings.—The appearances were only briefly recorded, but carcinomatous infiltration was present in both lungs and metastatic nodules were found in both kidneys. No further information is available.

Sections from the kidney (Figs 1 and 2) showed spheroidal cell carcinoma. The growth consisted of lobulated masses of large polygonal and columnar cells with granular eosinophilic cytoplasm, distinct cell boundaries, and large pale spheroidal nuclei. Mitoses were infrequent, and the cells, which were uniform in size, showed a distinct tendency to form tubules. There was an abundant dense fibrous stroma. Sections from the lung showed a similar picture.

Ocular Findings.—The left eye was fixed in Zenker's solution and opened by bilateral parasaggital section. Macroscopically, a flat yellowish-grey haemorrhagic tumour was present in the posterior choroid below the disc extending forward to the equator (Fig. 3, overleaf).

The degenerate retina was extensively detached. Section (Fig. 4, overleaf) showed a large spheroidal cell carcinomatous deposit, histologically identical with those in the lungs and kidney. The growth had invaded the sclera and extended along the intrascleral perivascular spaces, but there was no evidence of extra-ocular extension. Abundant haemorrhage was present in the choroid and in the subretinal space.

Discussion

Carcinomatous metastasis to the choroid from any primary site is a rare event. According to Stallard (1933) the incidence is 1 in 140,000 ophthalmic

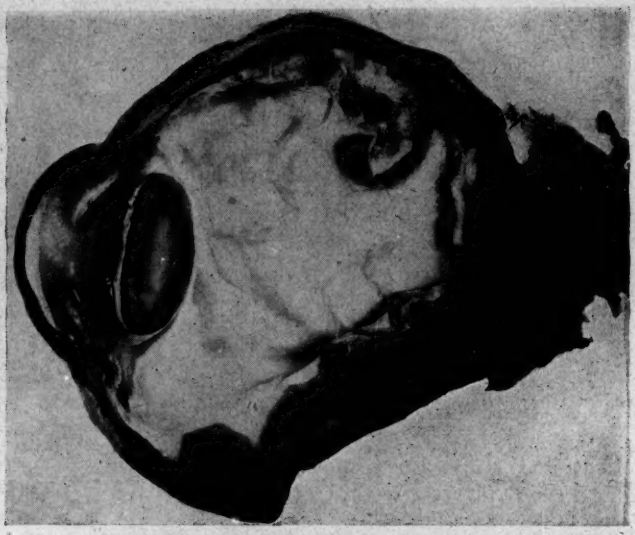

FIG. 3.—Parasaggital section of left eye. Zenker fixation. ×3.

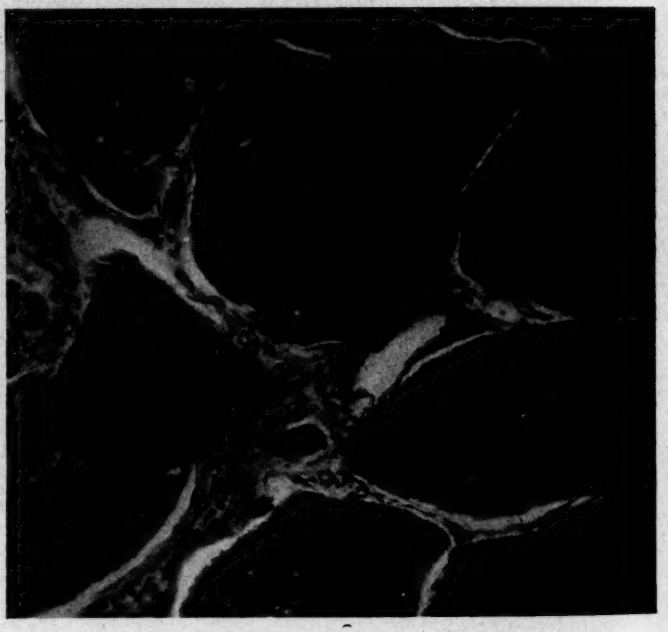

FIG. 4.—Metastatic spheroidal cell carcinoma in the choroid, from a primary in the male breast. Haematoxylin and eosin. ×120.

hospital patients, and the total of recorded cases was stated by Bedell (1943) to be 250. Over 50 per cent. of those recorded were of mammary origin.

Schinz (1939) saw only three cases with metastases in the choroid among 538 cases of mammary carcinoma treated at the Roentgen Institute in Zürich.

Previously unpublished figures from the archives of the Institute of Ophthalmology for the years 1935–53 show forty undoubted cases of metastatic carcinoma in the choroid. A further three probable cases in which there was some doubt about the histological diagnosis have been excluded, as have two metastases located principally in the anterior segment of the eye.

This series included 27 women and thirteen men; the average age of the women at enucleation was 51 years, that of the men 55.2 years. Of the forty cases, eighteen certainly and a further five probably, originated in the breast; seven cases (all men) were known to have pulmonary carcinoma, and in ten (five women and five men) no clinical evidence was presented to suggest the whereabouts or even the existence of a primary tumour at the time of enucleation. Histologically, 22 of the forty choroidal tumours were spheroidal cell carcinomata, two were oat cell secondaries from the lung, and the remaining ten adenocarcinomata.

By comparison, during the same length of time, the archives record 236 cases of retinoblastoma and 1,274 of malignant melanoma of the choroid.

Summary

The clinical and pathological findings in a case of metastatic carcinoma in the choroid from a primary in the male breast are briefly reported. The rarity of the condition is emphasized and some previously unpublished figures of the incidence of choroidal metastatic carcinoma from the records of the Institute of Ophthalmology are presented.

My thanks are due particularly to Dr. J. R. Acfield for permission to publish this case and for clinical details, to Dr. Peter Hansell for the photographs, and to Dr. Norman Ashton for advice.

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Brit. J. Ophthal. (1954) 38, 316.

LAMELLAR KERATOPLASTY FOLLOWED BY CATARACT EXTRACTION IN MALIGNANT PAPILLOMA OF THE LIMBUS*

BY

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THE treatment of epibulbar growths depends on several factors of which the extent of involvement of the globe itself is the most important; to some extent the line of treatment adopted depends not only on the preference of a particular surgeon but also on the facilities available. Lamellar keratoplasty has often been employed as a therapeutic measure and we have had some experience of it (Sivasubramaniam and Hoole, 1952). The idea of keratoplasty in new growths of the cornea is not new, for Lister (1951) has reported a case of corneo-scleral grafting in malignant melanoma invading the cornea. The following case illustrates the surgical and technical principles involved in the line of treatment adopted.

Case Report

A 48-year-old woman complained of loss of sight of one year's duration.

Examination.—On January, 7, 1953, each eye had a mature senile cataract. Vision in each was hand movements. The right eye showed in addition a greyish-white, horse-shoe shaped plaque-like growth, situated at the upper limbus and spreading on to the upper two-fifths of the cornea but sparing the pupillary area (Fig. 1). The growth, which was friable and bled easily on manipulation, was raised 0·5–1 mm. above the corneal surface and did not involve the deeper layers of the cornea. Neither the parotid nor the cervical lymph nodes were enlarged.

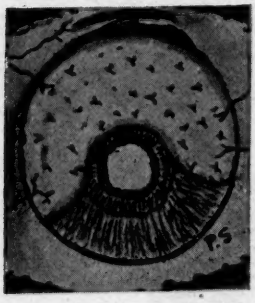

FIG. 1.—Growth riddled with blood vessels, clear cornea opposite pupil, and mature senile cataract.

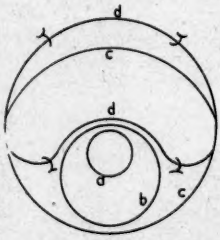

FIG. 2.—Diagram to illustrate operations: (a) pupillary border; (b) trephine mark; (c) limbus of host cornea; (d) outlines of growth and graft.

Operations

(*a*) Lamellar keratoplasty was done on January 14, 1953, under topical anaesthesia supplemented by retro-ocular novocaine. A freehand incision was made into the superficial layers of the cornea about 0·5 mm. away from the edge of the growth. The plaque was removed entire by performing a superficial keratectomy together with excision of the conjunctiva and episclera in the upper limbus. Bleeding was arrested by the application

*Received for publication December 28, 1953.

of hot probes. Next, while planning to cut the graft out of the donor eye it occurred to one of us (T.H.) that a 6-mm. keratoplasty trephine would fit into the " horns " of the horse-shoe shaped area (Fig. 2). The idea of cutting the graft by making measurements and freehand incision was, therefore, abandoned. A 6-mm. trephine with the scale set at 0·5 mm. was placed with its edge flush with the limbus and a cut made. A freehand incision was made along the rest of the limbus (Fig. 2). A Bock's lamellar keratoplasty knife was used to cut the lamella of cornea from the donor eye, starting from the limbus away from the trephine mark. The horse-shoe shaped lamella of cornea thus removed was transferred to the recipient bed and anchored by four sutures, two corneal and two corneo-conjunctival. Penicillin drops were instilled and the eye bandaged. Healing was uninterrupted. On the seventh day the sutures were removed and thereafter cortisone drops 0·5 per cent. were instilled to prevent neovascularization. The graft remained clear except at the upper limbus where a certain amount of haze was noticeable.

(*b*) Cataract extraction was performed on February 11, 1953; the right lens was extracted extracapsularly, and on March 13, 1953, the posterior capsule was needled.

Results.—When the patient left hospital on April 1, 1953, her vision was 6/36 with +10 D. sph. + 2 D. cyl., ax 180°.

Pathologist's Report.—The section is that of a malignant papilloma of the limbus.

Comment

The treatment of malignant papilloma of the limbus by excision is a feasible proposition owing to its low malignancy and superficiality. To leave a large area of cornea denuded after excision is not desirable and a corneal graft is obviously the best means of covering the area.

Difficulties in Operative Technique

The cutting of a large lamellar graft which is not circular presents great difficulties, the chief of which is the maintenance of uniformity in the thickness of the lamella. The matching of the shape of the graft to the recipient bed is an exercise in keratoplasty. The horns of the graft were missing to some extent. When the graft was reposed on its bed the former overlapped the upper limbus by 1 mm. Fortunately, though not by design, this fitted into a defect in the conjunctiva and episclera which was excised together with the growth. It would not have mattered if the graft had lain flush with the upper limbus as the conjunctiva could have been approximated by undermining. Direct suturing appeared to be the best method of fixing the graft. Small irregularities and defects in the edges of the graft, especially in the region of the " horns " epithelialized satisfactorily. Though the concave border of the graft was thicker, it united with the host border at the end of 3 weeks without leaving much evidence of a hump.

The next point of interest is the placing of the cataract section at the upper limbus. The knife was drawn out at the limbus, but during its traverse it cut the lamella of cornea that overlapped the sclera; the " feel " was different from usual because the knife encountered a little rigid corneal tissue instead of the soft conjunctiva. Though the wound did not gape easily and its lips were thick, extraction of the lens presented no difficulty, nor was there any delay in the healing of the wound.

Visual Result.—As is evident from the description and diagrams, this did not depend on the clarity of the graft; had the graft turned opaque the visual result would have been little affected, for the host cornea was clear opposite the pupil. The reason for the vision being in the order of 6/36 is to be found in the astigmatism induced by the grafting and the cataract extraction.

In this case the surgeon's preference and the available facilities prompted a certain line of treatment. Having no *x*-ray apparatus at our disposal we decided to excise the growth; and, having decided on this, we were happy indeed when a donor cornea was made available to us a few hours before operation.

We thank Dr. G. H. Cooray, Reader in Pathology, University of Ceylon, for reporting on the biopsy specimen, and Dr. C. M. Vanniasegeram, Medical Officer-in-Charge of the Jaffna Civil Hospital, for permission to publish this report.

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CORRESPONDENCE

VENTILATED GLASS CONTACT LENSES

To the Editorial Committee of the BRITISH JOURNAL OF OPHTHALMOLOGY

DEAR SIRS—I wonder if I may briefly comment on Mr. D. P. Choyce's paper on ventilated contact lenses (*British Journal of Ophthalmology*, **37**, 100) in explanation of what might appear to be rather contradictory statements.

We read on p. 109 (8) that " discomfort does not appear to be any less in the ventilated lenses ", and on p. 110 (9) that " veiling is almost as common with the ventilated type of lens "; yet statistical evidence shows that " an overwhelming majority of the patients who have worn both types prefer ventilated lenses " (p. 112 (5)).

When discussing discomfort, Choyce refers to its statistical incidence, not to its degree. The evidence that the permanent use of contact lenses, previously two in three, has improved to four in five since ventilation was introduced (Table VI, p. 107) is proof positive on this score. It might be of further help, perhaps, if I add that perforating anatomically-fitted unventilated lenses, as was the starting stage in 1946, results in comparative discomfort in nearly all cases, and that it took some years before the requirements of functional haptics, as set out on p. 105, reached the present level. As all our clinical material, from the very first experimental cases, was pooled for the enquiry, it follows that discomfort in the early days must show in the final figures (Table XXI-XXII), however low the more recent rate of incidence. The author's statement about his own intolerance (p. 114) is not based on the type of contact lens upon which his survey is written.

Regarding veiling, Choyce rightly complains of the difficulty of using subjective reports for the statistical treatment of objective phenomena. However, Table XV offers excellent material for more exact analysis; Column 1 comprises cases of pre-corneal opacities (mostly froth, epithelial detritus, and mucous discharge), Columns 2 to 4, cases of epithelial oedema (Sattler's veil and *peau d'orange* veiling), Column 6 interstitial oedema and the " late " haloes (p. 105). Only Column 5 is doubtful, whereas Column 7 obviously refers to some pathetic reports of the near-blind who see as through a veil when without contact lenses. If Table XIV had been brought into correlation with Table XV, it would have shown that it is the late types of veiling (after 8 hours or more of continuous wear) that tend to persist the longest. Most pre-corneal opacities can be helped (*e.g.* froth by the use of castor oil, and mucous discharge by adequate treatment of its bacterial cause), and all early veiling can be prevented (see p. 105), and it is no great hardship to split up the day's wear into two separate periods of under 8 hours each, so it would appear that only an infinitesimal fraction of veiling exists for which no immediate remedy is available. This, I submit, is an important pointer towards the " entirely new ideas " the author postulates if further advances are to be made. If only it were common knowledge that it is wrong to leave contact lens wearers to their own resources, and common practice that all should call back at regular intervals for a routine check-up, the present rate and degree of success would be certain to rise materially.

May I finally point out some inaccuracies that affect me personally. Bier is stated as reporting on the effects of ventilation in 1943; this date is presumably quoted from his

account of his Patent 592055, applied for in 1945 but not published before 1947, so that, far from any report, not even any technical publication on ventilated contact lenses was in existence before my clinical findings appeared in your Journal in 1946.

Also, the statement that I am responsible for training the fitters " working in other centres " should read " working in other centres under the same auspices ".

I am, Sirs,
Yours obediently,
J. DALLOS

CONTACT LENS CENTRE,
18 CAVENDISH SQUARE,
LONDON, W.1.

February 20, 1954.

BOOK REVIEW

Virus Diseases in Man. (Viruserkrankungen des Menschen). BY W. D. GERMER. 1954. Pp. 190, 47 figs (including 8 col.). G. Thieme Verlag, Stuttgart (30 DM.; 52*s.* 6*d.*).

This book comprises a useful short summary of modern knowledge on virus diseases the more common of which are considered seriatim after a useful preliminary review of the techniques of investigating and cultivating these organisms. Of the general virus diseases many, such as those responsible for measles, smallpox, polioencephalitis, encephalitis, molluscum contagiosum, herpes simplex and zoster, and so on, have a considerable ophthalmological interest, sometimes incidental, sometimes very real; others, such as those responsible for trachoma, inclusion blennorrhoea, and epidemic kerato-conjunctivitis, are peculiar to the province of this specialty. These are all briefly discussed with short bibliographies of the more important literature.

BOOKS RECEIVED

Biologie du cristallin (Report presented to the *Société française d'ophtalmologie*). By J. Nordmann. 1954. Pp. 730, 169 figs, 39 tables, bibl. Masson, Paris.

As an extensive review of this book will appear in *Ophthalmic Literature*, it is not proposed to make it the subject of a review in this Journal.

NOTES

THE ILLUMINATING ENGINEERING SOCIETY has conferred Honorary Membership upon Sir John Herbert Parsons who is a past-president of the Society and was the first chairman of its Council.